AN 1986:623647 CAPLUS
DN 105:223647
TI Induction of vascular relaxation by hydroperoxides
AU Thomas, George; Ramwell, Peter
CS Med. Cent., Georgetown Univ., Washington, DC, USA
SO Biochemical and Biophysical Research Communications (1986), 139(1), 102-8
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB H2O2, tert-Bu hydroperoxide, cumene hydroperoxide, 3-chloroperoxybenzoic acid (CPB), and 15-hydroperoxyeicosatetraenoic acid (15-HPETE) relaxed, in a concn.-dependent manner, rat aortic rings contracted with PGF2.alpha. (1 .times. 10-5M). Relaxation is not inhibited by either indomethacin (2 .times. 10-5M), a cyclooxygenase inhibitor, or eicosatetraynoic acid (1 .times. 10-5M), a dual cyclooxygenase and lipoxygenase inhibitor. Rings with intact endothelium relaxed to a greater degree on exposure to CPB and 15HPETE. **Methylene blue**, a sol. guanylate cyclase inhibitor (1 .times. 10-5M) blocked the relaxation elicited by the 5 **peroxides**, whereas both superoxide dismutase (scavenger of O2-) and mannitol (scavenger of OH radical) have no effect. Thus, relaxation of vascular smooth muscle is a general property of peroxides, and the endothelium may in some instances facilitate this effect.

AN 1996:308649 CAPLUS
DN 125:9418
TI Linoleic acid intake and susceptibility of very-low-density and low-density lipoproteins to oxidation in men
AU Louheranta, Anne M.; Porkkala-Sarataho, Elina K.; Nyyssonen, M. Kristiina; Salonen, Riitta M.; Salonen, Jukka T.
CS Research Institute Public Health, University Kuopio, Kuopio, 90211, Finland
SO American Journal of Clinical Nutrition (1996), 63(5), 698-703
CODEN: AJCNAC; ISSN: 0002-9165
PB American Society for Clinical Nutrition
DT Journal
LA English
AB Lipoprotein peroxidn. is thought to play an important role in atherogenesis. In the Kuopio **Atherosclerosis** Prevention Study (KAPS) the intake of fat and fatty acids, the oxidn. susceptibility of the plasma very-low-d. + low-d. lipoprotein (VLDL+LDL) fraction (by induction with copper or **hemin** and hydrogen **peroxide**), and concns. of plasma antioxidants, serum lipids, and lipoproteins were measured in 393 men. In the multivariate-regression model dietary linoleic acid was the most important determinant of the maximal oxidn. velocity for the hemin assay (standardized regression coeff. = 0.294, $P < 0.0001$). In the copper assay the assocn. of dietary linoleic acid and maximal oxidn. velocity was second in order of strength (standardized regression coeff. = 0.324, $P < 0.0001$). We conclude that high linoleic acid intake is assocd. with increased oxidn. susceptibility of atherogenic lipoproteins in men.

AN 1992:122794 CAPLUS
DN 116:122794
TI Hydrogen **peroxide**-induced pulmonary vasodilation: role of guanosine 3',5'-cyclic monophosphate
AU Burke-Wolin, Theresa; Abate, Charles J.; Wolin, Michael S.; Gurtner, Gail H.
CS Dep. Med., New York Med. Coll., Valhalla, NY, 10595, USA
SO American Journal of Physiology (1991), 261(6, Pt. 1), L393-L398
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
TI Hydrogen **peroxide**-induced pulmonary vasodilation: role of guanosine 3',5'-cyclic monophosphate
AB H2O2, but not tert-Bu hydroperoxide, produces a concn.-dependent vasodilation of the pulmonary circulation in isolated saline perfused rabbit lungs when pulmonary arterial pressures (PAP) are raised with the thromboxane analog U-46619. This vasodilation was enhanced in the presence of indomethacin, suggesting that H2O2 possesses both a prostaglandin-mediated constrictor and an addnl. dilator mechanism. In isolated rabbit intrapulmonary arteries the endothelium did not alter the dose-dependent relaxation of arterial rings to H2O2, and indomethacin enhanced the relaxant response of the **peroxide**. The decrease in PAP and relaxation of isolated pulmonary **arteries** obsd. with H2O2 was attenuated with 10 .mu.M **methylene blue**, an inhibitor of sol. guanylate cyclase activation. M & B 22948, a cGMP-selective phosphodiesterase inhibitor, enhanced the vasodilation or relaxation to the **peroxide** in both prepns. These changes were not endothelium dependent. Inhibition of the cGMP-assocd. endothelium-derived relaxant factor (EDRF) with nitro-L-arginine, did not alter relaxation of arterial rings to **peroxide**. Thus, H2O2 appears to produce pulmonary vasodilation through the activation of guanylate cyclase and accumulation of cGMP. Both H2O2 and EDRF may function as tonic stimulators of guanylate cyclase in the pulmonary circulation and contribute to the maintenance of low basal pressures.

AN 1992:122794 CAPLUS
DN 116:122794
TI Hydrogen **peroxide**-induced pulmonary vasodilation: role of guanosine 3',5'-cyclic monophosphate
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SO American Journal of Physiology (1991), 261(6, Pt. 1), L393-L398
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DT Journal
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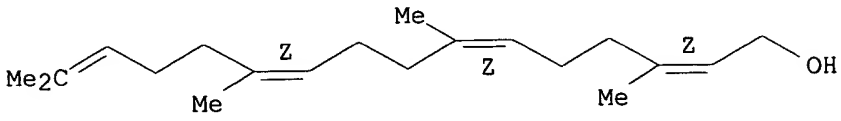
TI Hydrogen **peroxide**-induced pulmonary vasodilation: role of guanosine 3',5'-cyclic monophosphate
AB H2O2, but not tert-Bu hydroperoxide, produces a concn.-dependent vasodilation of the pulmonary circulation in isolated saline perfused rabbit lungs when pulmonary arterial pressures (PAP) are raised with the thromboxane analog U-46619. This vasodilation was enhanced in the presence of indomethacin, suggesting that H2O2 possesses both a prostaglandin-mediated constrictor and an addnl. dilator mechanism. In isolated rabbit intrapulmonary arteries the endothelium did not alter the dose-dependent relaxation of arterial rings to H2O2, and indomethacin enhanced the relaxant response of the **peroxide**. The decrease in PAP and relaxation of isolated pulmonary **arteries** obsd. with H2O2 was attenuated with 10 .mu.M **methylene blue**, an inhibitor of sol. guanylate cyclase activation. M & B 22948, a cGMP-selective phosphodiesterase inhibitor, enhanced the vasodilation or relaxation to the **peroxide** in both prepns. These changes were not endothelium dependent. Inhibition of the cGMP-assocd. endothelium-derived relaxant factor (EDRF) with nitro-L-arginine, did not alter relaxation of arterial rings to **peroxide**. Thus, H2O2 appears to produce pulmonary vasodilation through the activation of guanylate cyclase and accumulation of cGMP. Both H2O2 and EDRF may function as tonic stimulators of guanylate cyclase in the pulmonary circulation and contribute to the maintenance of low basal pressures.

RN 1945-42-2 REGISTRY
CN 2,6,10,14-Hexadecatetraen-1-ol, 3,7,11,15-tetramethyl-, (Z,Z,Z)- (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Geranylgeraniol, (Z,Z,Z)-**
FS STEREOSEARCH
MF C20 H34 O
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CHEMINFORMRX, USPATFULL
(*File contains numerically searchable property data)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9 REFERENCES IN FILE CA (1962 TO DATE)
9 REFERENCES IN FILE CAPLUS (1962 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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     FILE 'CAPLUS, WPIDS, MEDLINE' ENTERED AT 23:36:42 ON 23 FEB 2003
L4         9436 S (PEROXID? OR OXID? OR OZON?) (8A) (ALKENE# OR TERPEN? OR GERA

     FILE 'REGISTRY' ENTERED AT 23:38:07 ON 23 FEB 2003
L5            1 S DMSO/CN

     FILE 'CAPLUS, WPIDS, MEDLINE' ENTERED AT 23:38:20 ON 23 FEB 2003

     FILE 'REGISTRY' ENTERED AT 23:38:31 ON 23 FEB 2003
                SET SMARTSELECT ON
L6           SEL L5 1- CHEM :       30 TERMS
                SET SMARTSELECT OFF

     FILE 'CAPLUS, WPIDS, MEDLINE' ENTERED AT 23:38:32 ON 23 FEB 2003
L7         76026 S L6/BI
L8         53365 S PORPHYRIN# OR METALLOPORPHYRIN# OR FERROPORPHYRIN# OR HAEMATO
L9        207614 S BENZOQUINONE# OR ?QUINONE
L10            3 S L4 AND L7 AND L8 AND L9 <-- elected species
L11           70 S L4 AND L7
L12           67 S L11 NOT L10
L13       673456 S INFARCTION# OR MYOCARDIAL? OR CORONARY OR HEART DISEASE# OR A
L14            0 S L12 AND L13
L15            8 S L4 AND L13
L16            6 S L15 NOT L10
L17            5 DUP REM L16 (1 DUPLICATE REMOVED)

=> d que l8; d que l13
L8         53365 SEA PORPHYRIN# OR METALLOPORPHYRIN# OR FERROPORPHYRIN# OR
                 HAEMATOPORPHYRIN# OR HEMATOPORPHYRIN#


L13       673456 SEA INFARCTION# OR MYOCARDIAL? OR CORONARY OR HEART DISEASE#
                 OR ARTERIOSCLERO? OR ATHEROSCLERO? OR (BLOCKED (2A) ARTER?)
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     FILE 'CAPLUS, WPIDS, MEDLINE' ENTERED AT 23:36:42 ON 23 FEB 2003
L4         9436 S (PEROXID? OR OXID? OR OZON?) (8A) (ALKENE# OR TERPEN? OR GERA

     FILE 'REGISTRY' ENTERED AT 23:38:07 ON 23 FEB 2003
L5            1 S DMSO/CN

     FILE 'CAPLUS, WPIDS, MEDLINE' ENTERED AT 23:38:20 ON 23 FEB 2003

     FILE 'REGISTRY' ENTERED AT 23:38:31 ON 23 FEB 2003
                SET SMARTSELECT ON
L6           SEL L5 1- CHEM :       30 TERMS
                SET SMARTSELECT OFF

     FILE 'CAPLUS, WPIDS, MEDLINE' ENTERED AT 23:38:32 ON 23 FEB 2003
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L13       673456 S INFARCTION# OR MYOCARDIAL? OR CORONARY OR HEART DISEASE# OR A
L14            0 S L12 AND L13
L15            8 S L4 AND L13
L16            6 S L15 NOT L10
L17            5 DUP REM L16 (1 DUPLICATE REMOVED)

=> d que l8; d que l13
L8         53365 SEA PORPHYRIN# OR METALLOPORPHYRIN# OR FERROPORPHYRIN# OR
                 HAEMATOPORPHYRIN# OR HEMATOPORPHYRIN#


L13       673456 SEA INFARCTION# OR MYOCARDIAL? OR CORONARY OR HEART DISEASE#
                 OR ARTERIOSCLERO? OR ATHEROSCLERO? OR (BLOCKED (2A) ARTER?)


=> d que l4
L4          9436 SEA (PEROXID? OR OXID? OR OZON?) (8A) (ALKENE# OR TERPEN? OR
                 GERANIOL OR GERANYLGERANIOL)


=> s (ozon? or peroxid? or peroxy?) (l) l13
L18        8220 (OZON? OR PEROXID? OR PEROXY?) (L) L13

=> s l18 and l8
L19          19 L18 AND L8

=> dup rem l19
PROCESSING COMPLETED FOR L19
L20          18 DUP REM L19 (1 DUPLICATE REMOVED)
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Broader Searches

=> d 1-3 bib ab kwic

L10 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 2002:777646 CAPLUS
DN 137:284357
TI Targeted oxidative therapeutic formulation for arteriosclerosis treatment
IN Carpenter, Robert H.
PA Hofmann, Robert F., USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002078623	A2	20021010	WO 2002-US9089	20020322
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002177585	A1	20021128	US 2001-822773	20010330
PRAI	US 2001-822773	A	20010330		

AB The use of a pharmaceutical formulation in treating coronary arteriosclerosis and a 2-component pharmaceutical formulation are disclosed. The pharmaceutical formulation contains peroxidic species or reaction products resulting from **oxidn.** of an **alkene**, such as **geraniol**, by an oxygen-contg. **oxidizing** agent, such as **ozone**; a penetrating solvent, such as **DMSO**, a dye contg. a chelated metal, such as **hematoporphyrin**; and an arom. redox compd., such as **benzoquinone**. A pharmaceutical formulation was prepd. by sparging an ozone/pure oxygen gas mixt. of 120 mg/L up through geraniol at 1 L gas/h, maintaining the temp. at 5.degree., stopping the reaction when more than about 50% of the available unsatd. bonds have been reacted, and dilg. the product mixt. **DMSO** (1:10) to give a soln. or dispersion. Prior to use in the target biol. system, a mixt. of **hematoporphyrin**, Rose Bengal, and **methylnaphthoquinone** dry powders was added to the soln. or dispersion in sufficient quantity to create a concn. of 20 .mu.M of each component dispersed therein when delivered to the target biol. system by saline i.v. infusion.
AB The use of a pharmaceutical formulation in treating coronary arteriosclerosis and a 2-component pharmaceutical formulation are disclosed. The pharmaceutical formulation contains peroxidic species or reaction products resulting from **oxidn.** of an **alkene**, such as **geraniol**, by an oxygen-contg. **oxidizing** agent, such as **ozone**; a penetrating solvent, such as **DMSO**, a dye contg. a chelated metal, such as **hematoporphyrin**; and an arom. redox compd., such as **benzoquinone**. A pharmaceutical formulation was prepd. by sparging an ozone/pure oxygen gas mixt. of 120 mg/L up through geraniol at 1 L gas/h, maintaining the temp. at 5.degree., stopping the reaction when more than about 50% of the available unsatd. bonds have been reacted, and dilg. the product mixt. **DMSO** (1:10) to give a soln. or dispersion. Prior to use in the target biol. system, a mixt. of **hematoporphyrin**, Rose Bengal, and **methylnaphthoquinone** dry powders was added to the soln. or dispersion in sufficient quantity to create a concn. of 20 .mu.M of each component dispersed therein when delivered to the target biol. system by saline i.v. infusion.

ST oxidative therapeutic arteriosclerosis; **alkene peroxide oxidative** therapeutic arteriosclerosis

IT **Alkenes**, biological studies
Isoprenoids
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(targeted **oxidative** therapeutic formulation for arteriosclerosis treatment)

IT Chlorophyllins
Corrinoids
Fats and Glyceridic oils, biological studies
Glycerophospholipids
Lecithins
Peroxides, biological studies
Porphyrins
Sterols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted oxidative therapeutic formulation for arteriosclerosis treatment)

IT 106-24-1, **Geraniol**
RL: FMU (Formation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); RACT (Reactant or reagent); USES (Uses)
(**ozonation**; targeted **oxidative** therapeutic formulation for arteriosclerosis treatment)

IT 50-81-7, Ascorbic acid, biological studies 56-49-5, Methylcholanthrene 57-55-6, Propylene glycol, biological studies 58-27-5 61-73-4, Methylene blue 64-17-5, Ethanol, biological studies **67-68-5**, **DMSO**, biological studies 67-71-0, Methylsulfonylmethane 83-88-5, Lactoflavin, biological studies 106-51-4, 2,5-Cyclohexadiene-1,4-dione, biological studies 130-15-4, 1,4-Naphthalenedione 517-28-2, Hematoxylin 536-59-4, Perillyl alcohol 548-04-9, Hypericin 553-24-2, Neutral red 2321-07-5, Fluorescein 7439-89-6, Iron, biological studies 7439-95-4, Magnesium, biological studies 7439-96-5, Manganese, biological studies 7440-24-6, Strontium, biological studies 7440-31-5, Tin, biological studies 7440-50-8, Copper, biological studies 7440-50-8D, Copper, reaction with sodium chlorophyllins 7440-56-4D, Germanium, oxides 9003-39-8, PVP 11121-48-5, Rose bengal 14459-29-1, **Hematoporphyrin** 16009-13-5, Hemin 16423-68-0, Erythrosin 17372-87-1, Eosin 189752-49-6, Texaphyrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted oxidative therapeutic formulation for arteriosclerosis treatment)

L10 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 2002:777645 CAPLUS
DN 137:284356
TI Targeted oxidative therapeutic formulation
IN Hofmann, Robert F.
PA USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002078622	A2	20021010	WO 2002-US9088	20020322

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003032677 A1 20030213 US 2001-823252 20010330

PRAI US 2001-823252 A 20010330

AB A pharmaceutical formulation contains peroxide species or reaction products resulting from **oxidn.** of an **alkene**, such as **geraniol**, by an oxygen-contg. **oxidizing** agent such as **ozone**; a penetrating solvent, such as **DMSO**, a dye contg. a chelated metal, such as **hematoporphyrin**; and a arom. redox compd., such as **benzoquinone**. The pharmaceutical formulation is used to treat horses infected with Sarcocystis protozoal infections. A pharmaceutical formulation was prepd. by sparging an ozone/pure oxygen gas mixt. of 120 mg/L up through geraniol at 1 L gas/h, maintaining the temp. at 5.degree., stopping the reaction when more than about 50% of the available unsatd. bonds have been reacted, and dilg. the product mixt. **DMSO** (1:10) to give a soln. or dispersion. Prior to use in the target biol. system, a mixt. of **hematoporphyrin**, Rose Bengal, and **methylnaphthoquinone** dry powders was added to the soln. or dispersion in sufficient quantity to create a concn. of 20 .mu.M of each component dispersed therein when delivered to the target biol. system by saline i.v. infusion.

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ST targeted oxidative therapeutic formulation; **alkene peroxide** targeted formulation

IT **Alkenes**, biological studies
Isoprenoids
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(targeted **oxidative** therapeutic formulation)

IT Chlorophyllins
Corrinoids
Fats and Glyceridic oils, biological studies
Glycerophospholipids
Lecithins
Peroxides, biological studies
Porphyrins
Sterols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted oxidative therapeutic formulation)

IT 106-24-1, **Geraniol**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(**ozonated**; targeted **oxidative** therapeutic formulation)

IT 50-81-7, Ascorbic acid, biological studies 56-49-5, Methylcholanthrene

57-55-6, Propylene glycol, biological studies 61-73-4, Methylene blue 64-17-5, Ethanol, biological studies **67-68-5, DMSO,** biological studies 67-71-0, Methylsulfonylmethane 83-88-5, Lactoflavin, biological studies 106-51-4, 2,5-Cyclohexadiene-1,4-dione, biological studies 130-15-4, 1,4-Naphthalenedione 517-28-2, Hematoxylin 536-59-4, Perillyl alcohol 548-04-9, Hypericin 553-24-2, Neutral red 2321-07-5, Fluorescein 7439-89-6, Iron, biological studies 7439-95-4, Magnesium, biological studies 7439-96-5, Manganese, biological studies 7440-24-6, Strontium, biological studies 7440-31-5, Tin, biological studies 7440-50-8, Copper, biological studies 7440-50-8D, Copper, reaction with sodium chlorophyllin 7440-56-4D, Germanium, reaction with oxides 9003-39-8, Polyvinylpyrrolidone 11121-48-5, Rose bengal 14459-29-1, **Hematoporphyrin** 16009-13-5, Hemin 16423-68-0, Erythrosin 17372-87-1, Eosin 29595-63-9 189752-49-6, Texaphyrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted oxidative therapeutic formulation)

L10 ANSWER 3 OF 3 WPIDS (C) 2003 THOMSON DERWENT
AN 2003-058391 [05] WPIDS
DNC C2003-014886
TI Article of manufacture useful in the treatment of coronary arteriosclerosis comprises peroxidic species, penetrating solvent, a dye containing chelated metal and an aromatic redox compound.
DC A96 B05
IN CARPENTER, R H; HOFMANN, R F
PA (CARP-I) CARPENTER R H; (HOFM-I) HOFMANN R F
CYC 100
PI WO 2002078623 A2 20021010 (200305)* EN 26p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2002177585 A1 20021128 (200305)
ADT WO 2002078623 A2 WO 2002-US9089 20020322; US 2002177585 A1 US 2001-822773 20010330
PRAI US 2001-822773 20010330
AB WO 200278623 A UPAB: 20030121
NOVELTY - An article of manufacture comprises a first container and a second container. The first container comprises liquid phase containing **peroxidic** species or reaction products resulting from **oxidation** of **alkene** by mixture of **ozone** and oxygen and penetrating solvent. The second container contains solid phase comprising dye containing chelated divalent or trivalent metal and aromatic redox compound.

DETAILED DESCRIPTION - An article of manufacture comprises a first container and a second container. The first container comprises liquid phase containing **peroxidic** species or reaction products resulting from **oxidation** of **alkene** by mixture of **ozone** and oxygen and penetrating solvent. The **alkene** has less than 35C. The second container contains solid phase comprising dye containing chelated divalent or trivalent metal and aromatic redox compound.

An INDEPENDENT CLAIM is included for treating a patient with coronary arteriosclerosis involving administering a pharmaceutical formulation comprising the peroxide species or the reaction product, penetration solvent, the dye and the aromatic redox compound.

ACTIVITY - Antiarteriosclerotic; Antianginal; Cardiant.

A 63-year old Caucasian female had a medical history of a two-vessel coronary artery bypass graft (CABG) followed by repeat of mammary artery graft. The patient had keloid scar formation. The patient was given a

formulation (test) comprising (wt.%): tetraoxane dimer of acetal **peroxide** from **ozonization** of **geraniol** (0.54), dimethylsulfoxide (**DMSO**) (98), hematoprophyrin (0.83), **methylnaphthoquinone** (0.24) and chlorophyllin sodium-copper salt (0.39). Prior to infusion of test solution, the patient reported using nitroglycerine (NTG) sublingual tablets (up to 30 per week). The patient was taken to emergency room every 2 - 3 weeks for intravenous NTG infusion to resolve angina. The patient then received six doses of the test formulation. The dose was test solution (1 cc) diluted in sterile normal saline (100 cc), infused over 20 minutes. Her sublingual angina therapy was down to one per week, with most weeks requiring no NTG at all. It was observed that the patient had not been to hospital for intravenous anti-angina NTG infusion since receiving her first infusion of the test formulation. The patient's keloid from her graft donor site on the left forearm virtually disappeared following her first two doses of the test formulation.

MECHANISM OF ACTION - None given.

USE - In the treatment of coronary arteriosclerosis (claimed) and angina, myocardial infarction.

ADVANTAGE - The article of manufacture provides an effective and new curative way for treatment of coronary arteriosclerosis.

Dwg.0/0

AB . . .

- An article of manufacture comprises a first container and a second container. The first container comprises liquid phase containing **peroxidic** species or reaction products resulting from **oxidation** of **alkene** by mixture of **ozone** and oxygen and penetrating solvent. The second container contains solid phase comprising dye containing chelated divalent or trivalent metal and. . .

- An article of manufacture comprises a first container and a second container. The first container comprises liquid phase containing **peroxidic** species or reaction products resulting from **oxidation** of **alkene** by mixture of **ozone** and oxygen and penetrating solvent. The **alkene** has less than 35C. The second container contains solid phase comprising dye containing chelated divalent or trivalent metal and aromatic. . . graft. The patient had keloid scar formation. The patient was given a formulation (test) comprising (wt.%): tetraoxane dimer of acetal **peroxide** from **ozonization** of **geraniol** (0.54), dimethylsulfoxide (**DMSO**) (98), hematoprophyrin (0.83), **methylnaphthoquinone** (0.24) and chlorophyllin sodium-copper salt (0.39). Prior to infusion of test solution, the patient reported using nitroglycerine (NTG) sublingual tablets. . .

TECH. . .

agent is a liquid, micelle membrane, emollient, plasma, vapor, aqueous solvent, fat, sterol, lecithin, phosphatide, ethanol, propylene glycol, methylsulfonylmethane or **dimethyl sulfoxide**. The aromatic redox compound is **benzoquinone** or **naphthoquinone**. The dye comprises **porphyrin**, rose bengal, chlorophyllin, hemin, corrin, texaphrin, methylene blue, hematoxylin, eosin, erythrosin, lactoflavin, anthracene dye, hypericin, methylcholanthrene, neutral red or fluorescein.. . .

=> d 1-5 bib ab kwic

L17 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2002:567003 CAPLUS
TI Study on the effect of some pure plant volatile oils on the affinity of native and oxidized LDL to its receptor on the adrenal cells
AU Naderi, G. A.; Asgary, S.; Ani, M.; Sarrafzadegan, N.; Safary, M. R.
CS Isfahan Cardiovascular Res. Center, Isfahan Univ. Med. Sci., Esfahan, Iran
SO Faslnamah-i Giyahan-i Daruyi (2002), 1(1), 13-20, 85
CODEN: GDYAB6
PB Pazoheshkada Gyahun Daroei Jahad Danshgahei
DT Journal
LA Persian
AB Accumulating evidence shows high plasma levels and preoxidn. of LDL display the key role in atherogenesis. When LDL is oxidized, the affinity of LDL to its receptor is decreased and via scavenger receptor on macrophages is being taken off. The resultant accumulation of ox-LDL in macrophages leads to the appearance of foam cells and fatty streak formation in the subendothelial cells of arterial wall. In this study, antioxidant properties of eight natural volatile oils include: Geraniol, Thymol, Pulegone, P-cymol, Linalool, Limonene, Eugenol, Anethol and its effect on the affinity of native and oxidized LDL to its receptor in bovine adrenal cells have been investigated in the presence of fluoresein isothiocyanate-labeled LDL. The results show that between volatile oils used in the study Eugenol and Thymol are the best compds. that were increased the affinity of native and oxidized LDL to its adrenal cells receptor. The effect of these compd. on **oxidized** LDL is Thymol > Eugenol > **Geraniol** > Limonene > P-Cymol > Linalool > Anethol > Pulegone. And on native LDL is Eugenol > Thymol > Linalool > P-Cymol > Limonene > Geraniol > Pulegone > Anethol. These results indicate that, volatile oils esp. Thymol and Eugenol have antioxidant properties and probably via its lipophilic effect and effect on the LDL particles changed the affinity of LDL for its receptor. However, deeper and more studies are warranted to use such compds. for clin. usages, esp. **atherosclerosis** and cholesterol redn.
AB Accumulating evidence shows high plasma levels and preoxidn. of LDL display the key role in atherogenesis. When LDL is oxidized, the affinity of LDL to its receptor is decreased and via scavenger receptor on macrophages is being taken off. The resultant accumulation of ox-LDL in macrophages leads to the appearance of foam cells and fatty streak formation in the subendothelial cells of arterial wall. In this study, antioxidant properties of eight natural volatile oils include: Geraniol, Thymol, Pulegone, P-cymol, Linalool, Limonene, Eugenol, Anethol and its effect on the affinity of native and oxidized LDL to its receptor in bovine adrenal cells have been investigated in the presence of fluoresein isothiocyanate-labeled LDL. The results show that between volatile oils used in the study Eugenol and Thymol are the best compds. that were increased the affinity of native and oxidized LDL to its adrenal cells receptor. The effect of these compd. on **oxidized** LDL is Thymol > Eugenol > **Geraniol** > Limonene > P-Cymol > Linalool > Anethol > Pulegone. And on native LDL is Eugenol > Thymol > Linalool > P-Cymol > Limonene > Geraniol > Pulegone > Anethol. These results indicate that, volatile oils esp. Thymol and Eugenol have antioxidant properties and probably via its lipophilic effect and effect on the LDL particles changed the affinity of LDL for its receptor. However, deeper and more studies are warranted to use such compds. for clin. usages, esp. **atherosclerosis** and cholesterol redn.

L17 ANSWER 2 OF 5 MEDLINE
AN 2001669839 MEDLINE
DN 21573061 PubMed ID: 11715632
TI Antioxidative effects of lemon oil and its components on copper induced oxidation of low density lipoprotein.

AU Grassmann J; Schneider D; Weiser D; Elstner E F
CS Department of Plant Sciences, Institute of Pytopathology, Laboratory for Applied Biochemistry, Munich Technical University, Freising-Weihenstephan, Germany.
SO ARZNEIMITTEL-FORSCHUNG, (2001 Oct) 51 (10) 799-805.
Journal code: 0372660. ISSN: 0004-4172.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011122
Last Updated on STN: 20020124
Entered Medline: 20011228
AB Oxidation of low density lipoprotein (LDL) has been implicated in atherogenesis since several years. Therefore many researchers are looking for potent antioxidants which are able to inhibit LDL-oxidation and thus lower the risk for **atherosclerosis**. In particular several flavonoids have been investigated for their antioxidant capacity and it was shown that many factors influence the ability of flavonoids to retard LDL-oxidation, among others their lipophilic character. Since essential oils and some of their components which are highly lipophilic, have been shown to possess antioxidant properties, their effects on copper-induced LDL-**oxidation** were analysed. Plasma was incubated with different **terpenoid** substances and subsequently the LDL was isolated. It could be demonstrated that the terpenoids were enriched in LDL after incubation with plasma. To follow the kinetics of copper induced LDL-oxidation formation of conjugated dienes as well as loss of tryptophan fluorescence were measured. Furthermore the antioxidants alpha-tocopherol, beta-carotene and lycopene were quantified in LDL. It could be shown that particularly lemon oil and one of its components, gamma-terpinene, are efficiently slowing down the oxidation of LDL. This effect is independent of alpha-tocopherol stability in LDL, whereas the loss of carotenoids during oxidation is strongly retarded.
AB . . . Therefore many researchers are looking for potent antioxidants which are able to inhibit LDL-oxidation and thus lower the risk for **atherosclerosis**. In particular several flavonoids have been investigated for their antioxidant capacity and it was shown that many factors influence the. . . and some of their components which are highly lipophilic, have been shown to possess antioxidant properties, their effects on copper-induced LDL-**oxidation** were analysed. Plasma was incubated with different **terpenoid** substances and subsequently the LDL was isolated. It could be demonstrated that the terpenoids were enriched in LDL after incubation. . .

L17 ANSWER 3 OF 5 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-146805 [15] WPIDS
DNC C2001-043358
TI Cyclopentane derivatives substituted by cyclic amines e.g. piperidine, useful for modulating chemokine receptor activity and treating HIV, AIDS and inflammatory and immunoregulatory disorders e.g. **atherosclerosis** and asthma.
DC B02 B03 C02
IN CHAPMAN, K T; FINKE, P E; MACCOSS, M; MILLS, S G; OATES, B
PA (MERI) MERCK & CO INC
CYC 92
PI WO 2000076512 A1 20001221 (200115)* EN 2p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000054734 A 20010102 (200121)
US 6500844 B1 20021231 (200305)

ADT WO 2000076512 A1 WO 2000-US15755 20000608; AU 2000054734 A AU 2000-54734 20000608; US 6500844 B1 Provisional US 1999-139067P 19990611, US 2000-590487 20000608

FDT AU 2000054734 A Based on WO 200076512

PRAI US 1999-139067P 19990611; US 2000-590487 20000608

AB WO 200076512 A UPAB: 20011129

NOVELTY - Cyclopentane derivatives (I) and their salts and diastereoisomers are new.

DETAILED DESCRIPTION - Cyclopentane derivatives of formula (I) and their salts and diastereoisomers are new.

X = -(CO)NR9-, -NR9(CO)-, -O(CO)NR9-, -NR9(CO)O- or -NR9(CO)NR10-;

R9 = H, 1-10C alkyl, 3-8C cycloalkyl, 1-6C alkyl(3-6C) cycloalkyl, 2-10C alkenyl, 2-10C alkynyl, benzyl, phenyl or naphthyl optionally substituted by 1-3 of halo, OH, 1-6C alkyl, 1-3C alkoxy, phenyl or trifluoromethyl;

R10 = H, 1-6C alkyl, benzyl or phenyl optionally substituted by 1-3 of halo, 1-3C alkyl, 1-3C alkoxy and trifluoromethyl;

R9 + R10 = a 5-8 membered ring optionally substituted by halo, 1-3C alkyl, or 1-3C alkoxy;

Y = a single bond, -C(O)-, -C(O)O-, -SO2-, -SO2NR9-, 1-10C alkyl, -C(O)NR9- and -(CS)NR9-;

Q = a single bond, NR9, O or 1-10C alkyl;

R1 = phenyl, naphthyl, heterocycle other than tetrazolyl, 1-10C alkyl, 3-6C cycloalkyl, 1-6C alkyl(3-6C) cycloalkyl, 2-10C alkenyl, 2-10C alkynyl, 1-4C alkyl-phenyl or 1-4C alkyl-heterocycle optionally substituted by 1-3 of halo, 1-3C alkyl, 1-3C alkoxy, trifluoromethyl or trifluoromethoxy or when Q is NR9, then R9 and R1 may together form a 5-8 membered alkyl or heterocyclic ring optionally substituted by halo, 1-3C alkyl or 1-3C alkoxy;

R2 = H or OH, or R2 and Q may be joined together to form a double bond;

R3 = phenyl or heterocycle optionally substituted by 1-7 of halo, trifluoromethyl, OH, 1-3C alkyl, -O-(1-3C) alkyl, -CO2R9, -NR9R10 or -CONR9R10;

R7 = H, 1-6C alkyl optionally substituted by 1-4 of OH, CN or halo;

R8 = 1-10C alkyl, 3-6C cycloalkyl, 2-10C alkenyl, 2-10C alkynyl, phenyl, 1-6C alkyl-phenyl, 1-6C alkyl-(3-6C) cycloalkyl, 1-4C alkyl-O-(0-4C) alkyl-phenyl, naphthyl, biphenyl and heterocycle optionally substituted by 1-7 of R12;

R12 = halo, CN, OH, 1-6C alkyl optionally substituted by 1-5 of R13, -O-(1-6C) alkyl optionally substituted by 1-5 of R13, -CF3, -CHF2, -CH2F, -NO2, phenyl, -CO2R9, tetrazolyl, -NR9R10, -NR9-COR10, -NR9-CO2R10, -CO-NR9R10, -OCO-NR9R10, -NR9-COR9R10, -S(O)m-R9, -S(O)2-NR9R10, -NR9S(O)2-R10, -NR9S(O)2-NR9R10, 1-naphthyl or 2-naphthyl;

R13 = halo, CN, OH, 1-6C alkoxy, -CO2H, -CO2(1-6C alkyl), phenyl, trifluoromethyl and NR9R10; and

m, x, y = 0-2 provided that x + y is 2.

INDEPENDENT CLAIMS are also included for methods for:

(1) modulation of chemokine receptor activity in a mammal comprising the administration of (I);

(2) preventing and treating infection by HIV or treating or delaying the onset of AIDS comprising the administration of (I);

(3) prevention or treatment of an inflammatory and immunoregulatory disorder or disease comprising administration of (I); and

(4) prevention or treatment of asthma, allergic rhinitis, dermatitis, conjunctivitis, **atherosclerosis** or rheumatoid arthritis comprising the administration of (I).

ACTIVITY - Anti-HIV; antiarteriosclerotic; antiinflammatory; dermatological; antiarthritic; anti-AIDS, immunoregulatory; antiasthmatic; antiallergic; ophthalmological; cytostatic; antiparasitic; vasotropic; osteopathic; immunosuppressive; antithyroid; nephrotropic; antidiabetic;

neuroprotective; antipsoriatic; antirheumatic; antibacterial.

MECHANISM OF ACTION - (I) are modulators of chemokine receptor activity (preferably chemokine receptor antagonists), including CCR-5 and/or CCR-3, and inhibit the entry of human immunodeficiency virus (HIV) into target cells.

USE - (I) are used to modulate chemokine receptor activity in a mammal, to prevent and treat infection by human immunodeficiency virus (HIV), to treat or delay the onset of acquired immune deficiency syndrome (AIDS), to prevent or treat inflammatory and immunoregulatory disorders or diseases and to prevent or treat asthma, allergic rhinitis, dermatitis, conjunctivitis, **atherosclerosis** or rheumatoid arthritis (claimed).

(I) are also used in the treatment of other respiratory diseases such as hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g. Loeffler's syndrome, chronic eosinophilic pneumonia, delayed-type hypersensitivity, interstitial lung diseases (ILD) (e.g. idiopathic pulmonary fibrosis or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyosistis). (I) may also be used to treat systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g. to penicillin or cephalosporins) insect sting allergies, automimmune diseases such as rheumatiod arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myesthenia gravis, juvenile onset diabetes, glomerulonephritis, autoimmune thyroiditis, Behcet' disease, graft rejection, inflammatory bowel diseases such as Crohn's disease,and ulcerative colitis, spondyloarthropathies, scleroderma, psoriasis, inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria, vasculitis, esinophilic myositis, esinophilic fasciitis, cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions can be treated including reperfusion injury, **atherosclerosis**, certain hematologic malignancies, cytokine induced toxicity (e.g. septic shock, endotoxic shock), polymyositis, dermatomysitis, immunosupression, e.g. in those with AIDS or undergoing radiation therapy or chemotherapy, congenital deficiences and infectious diseases such as parasitic diseases including helminth infections by nematodes (round worms e.g. Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis), trematodes (flukes e.g. Schistosomiasis Clonorchiasis), cestodes (tapeworm e.g. Echinococcosis, Taeniasis saginata, Cysticercosis), visceral worms, visceral larva migrans (e.g. Toxicara), esinophilic gastroenteritis and cutaneous larva migrans.

(I) can also be used in the preparation and excecution of screening assays for compounds which modulate chemokine receptor activity e.g. (I) are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. (I) are also useful in establishing or determining the binding site of other compounds to chemokine receptors e.g. by competitive inhibition and are also useful for the evaluation of putative specific modulators of the chemokine receptors including CCR-5 and/or CCR-3.

Dwg.0/0

TI . . . cyclic amines e.g. piperidine, useful for modulating chemokine receptor activity and treating HIV, AIDS and inflammatory and immunoregulatory disorders e.g. **atherosclerosis** and asthma.

AB . . .

and immunoregulatory disorder or disease comprising administration of (I); and

(4) prevention or treatment of asthma, allergic rhinitis, dermatitis, conjunctivitis, **atherosclerosis** or rheumatoid arthritis comprising the administration of (I).

ACTIVITY - Anti-HIV; antiarteriosclerotic; antiinflammatory; dermatological; antiarthritic; anti-AIDS, immunoregulatory; antiasthmatic; antiallergic;. . . to prevent or treat inflammatory and immunoregulatory disorders or diseases and to prevent or treat asthma,

allergic rhinitis, dermatitis, conjunctivitis, **atherosclerosis** or rheumatoid arthritis (claimed).

(I) are also used in the treatment of other respiratory diseases such as hypersensitivity lung. . . fasciitis, cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions can be treated including reperfusion injury, **atherosclerosis**, certain hematologic malignancies, cytokine induced toxicity (e.g. septic shock, endotoxic shock), polymyositis, dermatomysitis, immunosupression, e.g. in those with AIDS or. . .

TECH UPTX: 20010317

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) may be prepared, for example, by **oxidation** of an **alkene** of formula (II) via **ozonolysis** to give a ketone of formula (III). (III) is then used to reductively alkylate an amine and the resulting amine. . .

TT TT: CYCLOPENTANE DERIVATIVE SUBSTITUTE CYCLIC PIPERIDINE USEFUL MODULATE RECEPTOR ACTIVE TREAT HIV AID INFLAMMATION DISORDER **ATHEROSCLEROSIS** ASTHMA.

L17 ANSWER 4 OF 5 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-514770 [46] WPIDS
DNC C2000-153571
TI New cyclic terpene compounds useful for stimulating melanogenesis in skin, hair, wool or fur, for treating proliferative disorders and treating neurodegenerative disorders or nerve damage.
DC B05 C03 D21
IN BROWN, D A; REN, W Y
PA (CODO-N) CODON PHARM INC
CYC 84
PI WO 2000044368 A1 20000803 (200046)* EN 39p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9942155 A 20000818 (200057)
ADT WO 2000044368 A1 WO 1999-US11841 19990528; AU 9942155 A AU 1999-42155 19990528
FDT AU 9942155 A Based on WO 200044368
PRAI US 1998-86547 19980528
AB WO 200044368 A UPAB: 20000921

NOVELTY - Cyclic terpene compounds (I) and (II) are new.

DETAILED DESCRIPTION - Cyclic terpene compounds of formula (I) and (II) are new.

A = optionally substituted cyclic terpene;

R1, R2, R8, R9 = OH;

R3, R4, R5, R6, R7, R10 = H or a linear or branched, cyclic, bicyclic or polycyclic group containing 1-50 atoms, at least one of which is C, N, O or S.

ACTIVITY - Cytostatic; antiseborrheic; dermatological; antipsoriatic; immuosuppressive; antiviral; neuroprotective; nootropic; anticonvulsant; neuroleptic; ophthalmological; cardiant; hypotensive; cerebroprotective; antidiabetic; hepatotropic; nephrotropic; vasotropic; analgesic; vulnerary.

MECHANISM OF ACTION - Melanogenesis stimulator; neuronal cell differentiation inducer; cellular nitric oxide synthase stimulator.

Compounds were formulated for application to human skin. 10 mu l of each formulation was applied twice daily for 10 days, followed by application of 10 mu l once per day for the remainder of the application period. Results show that (+)-2,2-dimethyl-3-hydroxy-3-hydroxymethyl-norbornane and (-)-2,2-dimethyl-3-(2,3-dihydroxy-propan-3-yl)-norbornane were 5- and 10-fold more potent, respectively, than (1R, 2R, 3S, 5R)-(-)-pinanediol with regards to induction of tanning when applied to

human skin for 14 days.

USE - Used for the stimulation of melanogenesis in mammalian skin, hair, wool, or fur (claimed). (I) And (II) can be used in the treatment of hypopigmentation disorders e.g. albinism or vitiligo, proliferative, tumorous or cancerous disorders in mammals e.g. actinic keratosis, basal cell carcinoma, squamous cell carcinoma, fibrous histiocytoma, dermatofibrosarcoma protuberans, hemagioma, nevus flammeus, xanothoma, Kaposi's sarcoma, mastocytosis, mycosis fungoides, lentigo nevocellular nevus, lentigo maligna, malignant melanoma, metastatic carcinoma, psoriasis vulgaris, psoriasis eosinophilia, acne vulgaris, acne conglobata, acne fulminans, osteoma cutis, nodulocystic acne and cystic acne, neurodegenerative disorders or nerve damage in mammals e.g. Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, diffuse cerebral cortical atrophy, Lewy-body dementia, Pick's disease, mesolimbocortical dementia, thalamic degeneration, Huntington's chorea, cortical-striatal-spinal degeneration, cortical-basal ganglionic degeneration, cerebrocerebellar degeneration, familial dementia with spastic paraparesis, polyglucosan body disease, Shy-Drager syndrome, olivopontocerebellar atrophy, progressive supranuclear palsy, dystonia musculorum deformans, Hallervorden-Spatz disease, Meige syndrome, familial tremors, Gilles de la Tourette syndrome, acanthocytic chorea, Friedreich ataxia, Holmes familial cortical cerebellar atrophy, Gerstmann-Straussler-Scheinker disease, progressive spinal muscular atrophy, progressive balbar palsy, primary lateral sclerosis, hereditary muscular atrophy, spastic paraplegia, peroneal muscular atrophy, hypertrophic interstitial polyneuropathy, heredopathia atactica polyneuritiformis, optic neuropathy and ophthalmoplegia. (I) And (II) can also be used for treating a disease regulated by the nitric oxide/cyclic GMP/protein kinase G pathway e.g. **heart disease**, hypertension, stroke, chronic obstructive pulmonary disease, adult respiratory distress syndrome, microvascular functional abnormalities in diabetes, hemostatic irregularities of glomerular vascular and tubular function, microvascular irregularities in the liver, disorders of bladder function and reflex relaxation for micturition, disorders of neurotransmitter release, neuron morphogenesis, synaptic plasticity, and neuroendrocrine regulation, migraine headaches, benign anal disease and impotence. (I) And (II) can also be used to stimulate wound healing.

Dwg.0/1

AB . . .

And (II) can also be used for treating a disease regulated by the nitric oxide/cyclic GMP/protein kinase G pathway e.g. **heart disease**, hypertension, stroke, chronic obstructive pulmonary disease, adult respiratory distress syndrome, microvascular functional abnormalities in diabetes, hemostatic irregularities of glomerular vascular. . .

TECH. . . .

of (I) comprises e.g. cis-hydroxylation of (+) and (-) camphene and (-)-beta-pinene with osmium tetroxide and hydrogen peroxide or N-methylmorpholine n-**oxide** in t-butanol to give a cyclic **terpene** compound of formula (I').

Preparation of (II) comprises e.g: hydroborating (-)-myrtenol to give the corresponding 3-exo alcohols which are then oxidized. . .

L17 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1

AN 1997:280249 CAPLUS

DN 126:338574

TI Cardioprotective and anti-**oxidant** effects of the **terpenoid** constituents of Ginkgo biloba extract (EGb 761)

AU Pietri, Sylvia; Maurelli, Eziana; Drieu, Katy; Culcasi, Marcel

CS Structure et Reactivite des Especes Paramagnetiques, Unite Mixte de Recherche 6517 du Centre National de la Recherche Scientifique, Univ. d'Aix-Marseille I et III, Marseille, F-13397, Fr.

SO Journal of Molecular and Cellular Cardiology (1997), 29(2), 733-742

CODEN: JMCDAY; ISSN: 0022-2828
PB Academic
DT Journal
LA English
AB Hemodynamic and ESR analyses were used to assess the in vivo and in vitro cardioprotective and antioxidant effects of therapeutically relevant doses of Ginkgo biloba ext. (EGb 761) and its terpenoid constituents (ginkgolides A and B, bilobalide) in the rat. Significant anti-ischemic effects, indicating improved **myocardial** functional recovery, were obsd. after repeated (15-day) oral treatments with both EGb 761 (60 mg/kg/day) and ginkgolide A (4 mg/kg/day), as compared to placebo. In vitro pre- and post-ischemic perfusion of hearts in the presence of the ginkgolides A and B (both at 0.05 .mu.g/mL) or bilobalide (0.15 .mu.g/mL), but not EGb 761 (5 .mu.g/mL) significantly improved all hemodynamic parameters. Post-ischemic levels of the 5,5-dimethyl-1-pyrroline N-oxide (DMPO)/hydroxyl radical spin-adduct (DMPO-OH) in **coronary** effluents were significantly decreased after in vivo oral treatments or after in vitro perfusion with EGb 761 or the terpenes, the most effective compd. being ginkgolide A. As the presence of the terpenes did not influence the formation of the superoxide/DMPO adduct or DMPO-OH in acellular tests with superoxide and hydroxyl radical generators, their cardioprotective effects appear to involve an inhibition of free radical formation rather than direct free radical scavenging.
TI Cardioprotective and anti-**oxidant** effects of the **terpenoid** constituents of Ginkgo biloba extract (EGb 761)
AB Hemodynamic and ESR analyses were used to assess the in vivo and in vitro cardioprotective and antioxidant effects of therapeutically relevant doses of Ginkgo biloba ext. (EGb 761) and its terpenoid constituents (ginkgolides A and B, bilobalide) in the rat. Significant anti-ischemic effects, indicating improved **myocardial** functional recovery, were obsd. after repeated (15-day) oral treatments with both EGb 761 (60 mg/kg/day) and ginkgolide A (4 mg/kg/day), as compared to placebo. In vitro pre- and post-ischemic perfusion of hearts in the presence of the ginkgolides A and B (both at 0.05 .mu.g/mL) or bilobalide (0.15 .mu.g/mL), but not EGb 761 (5 .mu.g/mL) significantly improved all hemodynamic parameters. Post-ischemic levels of the 5,5-dimethyl-1-pyrroline N-oxide (DMPO)/hydroxyl radical spin-adduct (DMPO-OH) in **coronary** effluents were significantly decreased after in vivo oral treatments or after in vitro perfusion with EGb 761 or the terpenes, the most effective compd. being ginkgolide A. As the presence of the terpenes did not influence the formation of the superoxide/DMPO adduct or DMPO-OH in acellular tests with superoxide and hydroxyl radical generators, their cardioprotective effects appear to involve an inhibition of free radical formation rather than direct free radical scavenging.
IT **Heart, disease**
(ischemia; cardioprotective and antioxidant effects of terpenoid constituents of Ginkgo biloba ext. (EGb 761) in heart ischemia)

L20 ANSWER 1 OF 18 MEDLINE
AN 2003079772 IN-PROCESS
DN 22479116 PubMed ID: 12591762
TI Potent **metalloporphyrin** peroxynitrite decomposition catalyst protects against the development of doxorubicin-induced cardiac dysfunction.
AU Pacher Pal; Liaudet Lucas; Bai Peter; Mabley Jon G; Kaminski Pawel M; Virag Laszlo; Deb Amitabha; Szabo Eva; Ungvari Zoltan; Wolin Michael S; Groves John T; Szabo Csaba
CS Inotek Pharmaceuticals Corp, Beverly, Mass 01915, USA.
NC R-43-CA-95807 (NCI)
R01-GM-36928 (NIGMS)
R01-HL-43023 (NHLBI)
R01-HL-59266 (NHLBI)
R43-CA-097559 (NCI)
SO CIRCULATION, (2003 Feb 18) 107 (6) 896-904.
Journal code: 0147763. ISSN: 1524-4539.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ED Entered STN: 20030221
Last Updated on STN: 20030221
TI Potent **metalloporphyrin** peroxynitrite decomposition catalyst protects against the development of doxorubicin-induced cardiac dysfunction.
AB BACKGROUND: Increased oxidative stress and dysregulation of nitric oxide have been implicated in the cardiotoxicity of doxorubicin (DOX), a commonly used antitumor agent. **Peroxynitrite** is a reactive oxidant produced from nitric oxide and superoxide in various forms of cardiac injury. Using a novel metalloporphyrinic **peroxynitrite** decomposition catalyst, FP15, and nitric oxide synthase inhibitors or knockout mice, we now delineate the pathogenetic role of **peroxynitrite** in rodent models of DOX-induced cardiac dysfunction. METHODS AND RESULTS: Mice received a single injection of DOX (25 mg/kg IP). Five days after DOX administration, left ventricular performance was significantly depressed, and high mortality was noted. Treatment with FP15 and an inducible nitric oxide synthase inhibitor, aminoguanidine, reduced DOX-induced mortality and improved cardiac function. Genetic deletion of the inducible nitric oxide synthase gene was also accompanied by better preservation of cardiac performance. In contrast, inhibition of the endothelial isoform of nitric oxide synthase with N-nitro-L-arginine methyl ester increased DOX-induced mortality. FP15 reduced the DOX-induced increase in serum LDH and creatine kinase activities. Furthermore, FP15 prevented the DOX-induced increase in lipid **peroxidation**, nitrotyrosine formation, and metalloproteinase activation in the heart but not NAD(P)H-driven superoxide generation. **Peroxynitrite** neutralization did not interfere with the antitumor effect of DOX. FP15 also decreased ischemic injury in rats and improved cardiac function and survival of mice in a chronic model of DOX-induced cardiotoxicity. CONCLUSIONS: Thus, **peroxynitrite** plays a key role in the pathogenesis of DOX-induced cardiac failure. Targeting **peroxynitrite** formation may represent a new cardioprotective strategy after DOX exposure or in other conditions associated with **peroxynitrite** formation, including **myocardial** ischemia/reperfusion injury.

L20 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
AN 2002:777646 CAPLUS
DN 137:284357
TI Targeted oxidative therapeutic formulation for arteriosclerosis treatment

IN Carpenter, Robert H.
PA Hofmann, Robert F., USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002078623	A2	20021010	WO 2002-US9089	20020322
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002177585	A1	20021128	US 2001-822773	20010330
PRAI	US 2001-822773	A	20010330		

AB The use of a pharmaceutical formulation in treating **coronary arteriosclerosis** and a 2-component pharmaceutical formulation are disclosed. The pharmaceutical formulation contains **peroxidic** species or reaction products resulting from oxidn. of an alkene, such as geraniol, by an oxygen-contg. oxidizing agent, such as **ozone**; a penetrating solvent, such as DMSO, a dye contg. a chelated metal, such as **hematoporphyrin**; and an arom. redox compd., such as benzoquinone. A pharmaceutical formulation was prepd. by sparging an **ozone** /pure oxygen gas mixt. of 120 mg/L up through geraniol at 1 L gas/h, maintaining the temp. at 5.degree., stopping the reaction when more than about 50% of the available unsatd. bonds have been reacted, and dilg. the product mixt. DMSO (1:10) to give a soln. or dispersion. Prior to use in the target biol. system, a mixt. of **hematoporphyrin**, Rose Bengal, and methylnaphthoquinone dry powders was added to the soln. or dispersion in sufficient quantity to create a concn. of 20 .mu.M of each component dispersed therein when delivered to the target biol. system by saline i.v. infusion.

ST oxidative therapeutic **arteriosclerosis**; alkene **peroxide** oxidative therapeutic **arteriosclerosis**

IT Chlorophyllins
Corrinoids
Fats and Glyceridic oils, biological studies
Glycerophospholipids
Lecithins
Peroxides, biological studies
Porphyrins
Sterols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted oxidative therapeutic formulation for **arteriosclerosis** treatment)

IT 106-24-1, Geraniol
RL: FMU (Formation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); RACT (Reactant or reagent); USES (Uses)
(**ozonation**; targeted oxidative therapeutic formulation for **arteriosclerosis** treatment)

IT 3352-57-6, Hydroxy, reactions 10028-15-6, **Ozone**, reactions 11062-77-4, Superoxide 13444-71-8, Periodic acid (HIO4) 14915-07-2, **Peroxide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(targeted oxidative therapeutic formulation for **arteriosclerosis** treatment)

IT 50-81-7, Ascorbic acid, biological studies 56-49-5, Methylcholanthrene 57-55-6, Propylene glycol, biological studies 58-27-5 61-73-4, Methylene blue 64-17-5, Ethanol, biological studies 67-68-5, DMSO, biological studies 67-71-0, Methylsulfonylmethane 83-88-5, Lactoflavin, biological studies 106-51-4, 2,5-Cyclohexadiene-1,4-dione, biological studies 130-15-4, 1,4-Naphthalenedione 517-28-2, Hematoxylin 536-59-4, Perillyl alcohol 548-04-9, Hypericin 553-24-2, Neutral red 2321-07-5, Fluorescein 7439-89-6, Iron, biological studies 7439-95-4, Magnesium, biological studies 7439-96-5, Manganese, biological studies 7440-24-6, Strontium, biological studies 7440-31-5, Tin, biological studies 7440-50-8, Copper, biological studies 7440-50-8D, Copper, reaction with sodium chlorophyllins 7440-56-4D, Germanium, oxides 9003-39-8, PVP 11121-48-5, Rose bengal 14459-29-1, **Hematoporphyrin** 16009-13-5, Hemin 16423-68-0, Erythrosin 17372-87-1, Eosin 189752-49-6, Texaphyrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted oxidative therapeutic formulation for arteriosclerosis treatment)

L20 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2003 ACS
AN 2002:220551 CAPLUS
DN 136:246398
TI Methods and compositions using antioxidant for reducing antibody-mediated generation of hydrogen peroxide and superoxide and oxidative stress
IN Wentworth, Paul; Wentworth, Anita D.; Jones, Lyn H.; Janda, Kim D.; Lerner, Richard A.
PA The Scripps Research Institute, USA
SO PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002022573	A2	20020321	WO 2001-US29165	20010917
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002012970	A5	20020326	AU 2002-12970	20010917
PRAI	US 2000-232702P	P	20000915		
	US 2000-235475P	P	20000926		
	US 2001-315906P	P	20010829		
	WO 2001-US29165	W	20010917		

IT **Heart, disease**
Intestine, disease
(ischemia; methods and compns. using antioxidant for reducing antibody-mediated generation of hydrogen **peroxide** and superoxide and oxidative stress)
IT 14459-29-1, **Hematoporphyrin**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. using antioxidant for reducing antibody-mediated generation of hydrogen peroxide and superoxide and oxidative stress)

L20 ANSWER 4 OF 18 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-241437 [29] WPIDS
DNC C2002-072597

TI New **metalloporphyrins** useful in the treatment of free radical associated diseases e.g. stroke.
DC B02
IN COSLEDAN, F; MEUNIER, B
PA (EUKA-N) EUKARION INC
CYC 96
PI WO 2002004454 A1 20020117 (200229)* EN 108p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001071987 A 20020121 (200234)
US 6403788 B1 20020611 (200244)
ADT WO 2002004454 A1 WO 2001-US21918 20010711; AU 2001071987 A AU 2001-71987 20010711; US 6403788 B1 US 2000-613891 20000711
FDT AU 2001071987 A Based on WO 200204454
PRAI US 2000-613891 20000711
TI New **metalloporphyrins** useful in the treatment of free radical associated diseases e.g. stroke.
AB WO 200204454 A UPAB: 20020513
NOVELTY - Non-genotoxic **metalloporphyrins** or their complexes with metal ions are new.

DETAILED DESCRIPTION - Non-genotoxic **metalloporphyrins** of formula (I) or their complexes with metal ions are new:

R1 - R4 = -SO2-NH-L-X+(R13)(R15)-R14 Y-;

L = 2-12C linker optionally interspersed with 1 - 4 heteroatoms selected from oxygen, nitrogen or sulfur;

X = nitrogen or phosphorus;

R13 - R15 = hydrogen, alkyl or arylalkyl;

Y- = monovalent anion;

R5 - R12 = H, alkyl or halo; and

R16 = at least one of hydrogen, hydroxy, halo or alkyl.

INDEPENDENT CLAIMS are also included for the following:

(a) compounds of formulae (II) - (VIII);

(b) preparation of (II) - (VIII); and

(c) use of (I) in the manufacture of a medicament for prophylaxis or treatment of a free radical associated disease.

ACTIVITY - Antioxidant; Cerebroprotective; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Cytostatic; Dermatological; Immunosuppressive; Antiinflammatory; Antipsoriatic; Antibacterial; Antiasthmatic; Antiallergic; Anti-HIV; Antiulcer; Antiarteriosclerotic; Hypotensive; Cardiant; Antiarthritic; Antirheumatic; Ophthalmological; Osteopathic.

MECHANISM OF ACTION - Superoxide dismutase (SOD), catalase (CAT) and/or **peroxidase** mimetics.

(SOD) activity was measured by incubating meso-tetrakis(3-(N-(2-(N,N,N-diethylmethylammonio)ethyl)aminosulfonyl)-2,4,6-trimethylphenyl)porphyrinato diaqua-manganese (III) pentaacetate (A1) with a superoxide generating system (xanthine, 60 micro M-xanthine oxidase, 0.009 units/ml) and cytochrome C (detector) (27.8 micro M). The IC50 value for (A1) was found to be 0.013 micro M.

USE - For the treatment of a free radical and oxyradical associated diseases e.g. stroke, Alzheimer's disease, dementia, Parkinson's disease, Lou Gehrig disease, motor neuron disorders, Huntington's disease, cancer, multiple sclerosis, systemic lupus erythematosus, scleroderma, eczema, dermatitis, delayed type hypersensitivity, psoriasis, gingivitis, adult respiratory distress syndrome, septic shock, multiple organ failure, inflammatory diseases, asthma, allergic rhinitis, pneumonia, emphysema, chronic bronchitis, AIDS, inflammatory bowel disease, gastric ulcers, pancreatitis, transplantation rejection, **atherosclerosis**, hypertension, congestive heart failure, **myocardial** ischemic

disorders, angioplasty, endocarditis, retinopathy of prematurity, cataract formation, uveitis, rheumatoid arthritis, oxygen toxicity, herpes simplex infection, burns, osteoarthritis and aging (all claimed). The compounds are also useful in the treatment of cardiac tissue necrosis due to cardiac ischemia, autoimmune neurodegeneration, acute lung injury and neuronal damage from ischemia; for preventing ischemia/reoxygenation injury; for preserving organs for transplant in an anoxic, hypoxic or hyperoxic state before transplant; for protecting normal tissue from exposure to ionizing radiation and/or chemotherapy with bleomycin; for protecting cells and tissues from exposure to xenobiotics; for enhancing cryopreservation of cells, tissues, organs and organisms by increasing viability of recovered specimens; for prophylactic administration to prevent carcinogenesis, cellular senescence, formation of malondialdehyde adducts, HIV pathology and macromolecular crosslinking (preferably collagen crosslinking).

ADVANTAGE - The compounds are non-genotoxic.

Dwg.0/2

TECH UPTX: 20020513

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (II) - (V) are prepared as follows:
(i) reacting a **porphyrin** derivative (A) with chlorosulfonic acid and further by N,N-diethylenediamine to form a first intermediate;
(ii) reacting the first intermediate with a metal salt (B) in presence of a hindered base to form a second intermediate; and
(iii) reacting the second intermediate with hydrochloric acid to form (II) - (V). (VI) - (VIII) are prepared as follows: step (i), (ii), (iv) reacting the second intermediate with methyl iodide to form a third intermediate; and
(v) reacting the third intermediate with AGI-X8 (acetate resin) to exchange the counter ion from iodide to acetate and form (VI) - (VIII).
(A) is meso-tetraphenyl **porphyrin** (for (II), (III) and (VI)) or meso-tetrakis(2,4,6-trimethylphenyl)**porphyrin** (for (IV), (V), (VII) and (VIII)). (B) is Mn(OAc)2, Fe(OAc)2 or ferrous chloride.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Complex: (I) forms a complex with metal ions selected from manganese, iron, cobalt, copper or zinc (preferably Mn(III), Fe(III), Co(III), Cu or Zn, especially iron or manganese). The metal ion is bonded to an additional anionic ligand selected from fluoro, chloro, bromo, iodido, hydroxy and ZCOO- (preferably hydroxyl, chloro or acetato).
Z = alkyl, aryl or arylalkyl.

L20 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2003 ACS
AN 2001:395173 CAPLUS
DN 135:120214
TI Inhibition of oxidized low-density lipoprotein-induced apoptosis in endothelial cells by nitric oxide. Peroxyl radical scavenging as an antiapoptotic mechanism
AU Kotamraju, Srigiridhar; Hogg, Neil; Joseph, Joy; Keefer, Larry K.; Kalyanaraman, B.
CS Biophysics Research Institute and Free Radical Research Center, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SO Journal of Biological Chemistry (2001), 276(20), 17316-17323
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Proatherogenic oxidized low-d. lipoprotein (ox-LDL) induces endothelial apoptosis. We investigated the anti-apoptotic effects of intracellular and extracellular nitric oxide (.cntdot.NO) donors, iron chelators, cell-permeable superoxide dismutase (SOD), glutathione peroxidase mimetics, and nitrone spin traps. Peroxynitrite (ONOO-)-modified oxLDL

induced endothelial apoptosis was measured by DNA fragmentation, TUNEL assay, and caspase-3 activation. Results indicated the following: (i) the lipid fraction of oxLDL was primarily responsible for endothelial apoptosis. (ii) Endothelial apoptosis was potently inhibited by .cntdot.NO donors and lipophilic phenolic antioxidants. OxLDL severely depleted Bcl-2 levels in endothelial cells, and .cntdot.NO donors restored Bcl-2 protein in oxLDL-treated cells. (iii) The pretreatment of a lipid fraction derived from oxLDL with sodium borohydride or potassium iodide completely abrogated apoptosis in endothelial cells, suggesting that lipid hydroperoxides induce apoptosis. (iv) **Metalloporphyrins** dramatically inhibited oxLDL-induced apoptosis in endothelial cells. Neither S-nitrosation of caspase-3 nor induction of Hsp70 appeared to play a significant role in the antiapoptotic mechanism of .cntdot.NO in oxLDL-induced endothelial apoptosis. We propose that cellular lipid peroxyl radicals or lipid hydroperoxides induce an apoptotic signaling cascade in endothelial cells exposed to oxLDL, and that .cntdot.NO inhibits apoptosis by scavenging cellular lipid peroxyl radicals.

ST **atherosclerosis** vascular endothelium apoptosis oxidized low density lipoprotein NO; endothelium apoptosis oxLDL lipid **peroxyl** radical hydroperoxide nitric oxide

IT **Atherosclerosis**
(endothelial injury in relation to; lipid **peroxyl** radicals or lipid hydroperoxides induce apoptosis in vascular endothelial cells exposed to oxidized low-d. lipoprotein and nitric oxide inhibits apoptosis by scavenging lipid **peroxyl** radicals)

L20 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2003 ACS
AN 2001:214577 CAPLUS
DN 135:1942
TI Mn(II)-Texaphyrin as a Catalyst for the Decomposition of Peroxynitrite
AU Shimanovich, Roman; Hannah, Sharon; Lynch, Vincent; Gerasimchuk, Nikolay; Mody, Tarak D.; Magda, Darren; Sessler, Jonathan; Groves, John T.
CS Department of Chemistry, Princeton University, Princeton, NJ, 08544, USA
SO Journal of the American Chemical Society (2001), 123(15), 3613-3614
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
OS CASREACT 135:1942
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Manganese and iron **porphyrins**, as well as other macrocyclic metal complexes, have recently been reported to be highly active catalysts for **peroxynitrite** decompn. **Peroxynitrite** anion, ONOO-, formed in vivo by combination of nitric oxide and superoxide anion, has been implicated as a cytotoxic agent in connection with numerous conditions and diseases including **atherosclerosis**, ALS, cancer, and ischemia-reperfusion injury. It is believed that **peroxynitrite** forms RNSs (reactive nitrogen species) during its decay into less reactive nitrate and nitrite anions, and it is these RNSs that react with biol. targets. Synthetic metal complexes that can act catalytically and safely to decomp. **peroxynitrite** without forming RNSs would constitute an important pharmacol. advance. This communication reports the synthesis of the first structurally characterized Mn(II)texaphyrin complex (Mn-Tex) and its ability to catalyze **peroxynitrite** decompn. without causing concomitant phenol nitration in aq. soln. at pH 7.4.

L20 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2003 ACS
AN 2001:506449 CAPLUS
TI Peroxynitrile decomposition catalysts and methods of use thereof
CS Princeton University: WO0075144
SO Expert Opin. Ther. Pat. (2001), 11(7), 1229-1231

CODEN: EOTPEG; ISSN: 1354-3776
PB Ashley Publications Ltd.
DT Journal
LA English
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Novel metal complexes of macrocyclic ligands, particularly substituted **porphyrin**, porphyrazine, texaphyrin, salen and corrole complexes and methods of their use for lowering **peroxynitrite** (PN) levels in the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, stroke, AIDS dementia, Huntington's chorea, **atherosclerosis**, chronic inflammation, autoimmune disease, cancer, ischemia-reperfusion injury, septic shock and chronic graft rejection are claimed. These metallic **peroxynitrite** decompn. catalysts are stated to have a high catalytic activity, high in vivo stability and half-life, an optimized tissue distribution and a low toxicity.

L20 ANSWER 8 OF 18 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-080578 [09] WPIDS
DNC C2001-023198
TI New 2-pyridyl-**porphyrins** are peroxynitrite decomposition catalysts, useful e.g. in treating Alzheimer's disease, amyotrophic lateral sclerosis, stroke, autoimmune diseases and cancer.
DC B02
IN GROVES, J T; MOELLER, S M
PA (UYPR-N) UNIV PRINCETON
CYC 94
PI WO 2000075144 A2 20001214 (200109)* EN 45p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000054603 A 20001228 (200119)
EP 1185532 A1 20020313 (200225) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
US 6448239 B1 20020910 (200263)
JP 2003501432 W 20030114 (200306) 54p
ADT WO 2000075144 A2 WO 2000-US15269 20000602; AU 2000054603 A AU 2000-54603 20000602; EP 1185532 A1 EP 2000-939526 20000602, WO 2000-US15269 20000602; US 6448239 B1 Provisional US 1999-137308P 19990603, US 2000-587382 20000601; JP 2003501432 W WO 2000-US15269 20000602, JP 2001-502426 20000602
FDT AU 2000054603 A Based on WO 200075144; EP 1185532 A1 Based on WO 200075144; JP 2003501432 W Based on WO 200075144
PRAI US 2000-587382 20000601; US 1999-137308P 19990603
TI New 2-pyridyl-**porphyrins** are peroxynitrite decomposition catalysts, useful e.g. in treating Alzheimer's disease, amyotrophic lateral sclerosis, stroke, autoimmune diseases and cancer.
AB WO 200075144 A UPAB: 20011129
NOVELTY - Metallic complexes of substituted 2-pyridyl-**porphyrins** (I)-(VII), their bases, acid addition salts, hydrates, esters, solvates, prodrugs, metabolites and/or stereoisomers are new.
DETAILED DESCRIPTION - Metallic complexes of substituted 2-pyridyl-**porphyrins** of formula (I)-(VII), their bases, acid addition salts, hydrates, esters, solvates, prodrugs, metabolites and/or stereoisomers are new.
At least one of R1- R4, A -D = (CH2)n-X, (CH2)n'-Y, Y2-C-(Z1)3, (CH2)p-C(O)-Y-C(Z2)3, (CH2)q-OCH2C(CH2OH) or (CH2)q-O-CH2C(CH2OH)2(H or Me) (sic);
n = 1-6;

X = CO2H, CONH2, CONR'2, PO3H2, SO3H, NH2, NR'2 or NR3+;
n' = 2;
Y = OH or (O-(CH2)2)m-W;
W = OH or (O-(CH2)2)m;
m = 1-200;
Z1 = CH2OCH2(CH2)p-X or Y';
Y' = (CH2)-N-O, (CH2)pNH or (CH2)pS;
p = 1-10;
Z2 = O-CHCHC-C(O)-Y-(C(Z3)3)p';
p' = 1-100;
Z3 = OCHCHC-C(O)-Y-C(Z4)3;
Z4 = OCHCHC-C-Z5;
Z5 = CO2H, CONH2, CONR'2, PO3H2, SO3H, NH2, NR'2 or NR'3+; and
M = Mn, Fe, Ni or V.
R' is not defined.

An INDEPENDENT CLAIM is also included for a complex of formula (I) where R1-R4 may also be (CH2)-C(H)=C(H), CH2CONH2, CH2CO2CH2Me or (CH2CH2O)2CH2CH2OMe.

ACTIVITY - Nootropic; neuroprotective; anti-HIV; antiinflammatory; immunosuppressive; anticonvulsant; antiarteriosclerotic; antibacterial; cytostatic; vulnerary; osteopathic; ophthalmological; neuroprotective; dermatological; antiarthritic; antiasthmatic; nephrotropic.

MECHANISM OF ACTION - None given.

USE - (I)-(VII) are used to lower **peroxynitrite** levels in a cell or tissue, and for the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, stroke, AIDS-related dementia, Huntington's disease, **atherosclerosis**, chronic inflammation, autoimmune diseases, cancer, ischemia-reperfusion injury, septic shock and chronic graft rejection (claimed). They can also be used as diagnostic probes to determine the involvement of **peroxynitrite** and other reactive oxygen and nitrogen species in disease states both in vivo and in vitro. They can be used to prevent or reduce cellular damage resulting from exposure to chemicals which produce potentially damaging free radical species. They may be administered for preventing ischemic reoxygenation injury in a patient, for preserving organs for transplant in an apoxic, hypoxic or hyperoxic state prior to transplant, for protecting normal tissue from free radical-induced damage following exposure to ionizing radiation and/or chemotherapy, as with bleomycin, for protecting cells and tissues from free radical-induced injury following exposure to xenobiotic compounds which form free radicals, either directly or as a consequence of monooxygenation through the cytochrome P-450 system and for enhancing cryopreservation of cells, tissues, organs and organisms by increasing viability of recovered specimens. They can be prophylactically administered to prevent carcinogeneisis, cellular senescence, cataract formation, formation of malondialdehyde adducts, HIV pathology and macromolecular crosslinking such as collagen crosslinking. They can be used to enhance the recovery of skin of warm blooded animals from wounds such as surgical incisions, burns, inflammation or minor irritation due to oxidative damage. Other diseases to be treated included disorders of the joints (e.g. arthritis), bone diseases associated with increased bone resorption, inflammatory bowel diseases (e.g. Crohn's disease), inflammatory lung diseases (e.g. asthma), inflammatory disorders of the eye (e.g. corneal dystrophy), chronic inflammatory disorders of the gum (e.g. gingivitis), tuberculosis, leprosy, inflammatory disorders of the kidney, skin, central nervous system and multiple sclerosis.

ADVANTAGE - (I)-(VII) have very low, if any toxicity. Since the degree to which **peroxynitrite** decomposition agents bind and cleave DNA is indicative of their cellular toxicity, the calf thymus-DNA titration of both 4-tetrakis(carboxamide)pyridyl **porphyrin** (4-T(CX)PyP) and 2-T(CX)PyP was carried out. It was found that in the case of 4-T(CX)PyP, there was a loss of intensity in the Soret band and a pronounced redshift, these being indicative of both **porphyrin** intercalation into DNA and outside stacking of **porphyrin** along

the DNA backbone. In the analogous titration with 2-T(CX)PyP, only a small change in the Soret band was observed which indicates little or no association with DNA. Even when CT-DNA was added in large excess to the solution of the **porphyrin**, a redshift of only 2 nM was observed. Further, upon treatment with oxidants such as hydrogen **peroxide**, oxone or **peroxynitrite**, the 2-pyridyl **porphyrins** caused much less DNA cleavage.
Dwg.0/6

L20 ANSWER 9 OF 18 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-482907 [42] WPIDS
DNC C2000-145375
TI New substituted **porphyrins** useful for e.g. treating conditions that result from or are exacerbated by oxidant-induced toxicity.
DC B02
IN BATINIC-HABERLE, I; CRAPO, J D; DAY, B J; FRIDOVICH, I; KITCHEN, D B; POLIVINI, J F; TROVA, M P; GAUUAN, P J F
PA (NAJE-N) NAT JEWISH MEDICAL & RES CENT; (AEOL-N) AEOLUS PHARM INC; (UYDU-N) UNIV DUKE; (AEOL-N) AEOLUS PHARMACEUTICALS INC
CYC 90
PI WO 2000043395 A1 20000727 (200042)* EN 77p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000027407 A 20000807 (200055)
BR 2000007720 A 20011030 (200173)
EP 1155019 A1 20011121 (200176) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
KR 2001108130 A 20011207 (200236)
CN 1355802 A 20020626 (200263)
JP 2002535332 W 20021022 (200301) 82p
ZA 2001006107 A 20021224 (200309) 89p
ADT WO 2000043395 A1 WO 2000-US2062 20000125; AU 2000027407 A AU 2000-27407 20000125; BR 2000007720 A BR 2000-7720 20000125, WO 2000-US2062 20000125; EP 1155019 A1 EP 2000-905776 20000125, WO 2000-US2062 20000125; KR 2001108130 A KR 2001-709367 20010725; CN 1355802 A CN 2000-805458 20000125; JP 2002535332 W JP 2000-594811 20000125, WO 2000-US2062 20000125; ZA 2001006107 A ZA 2001-6107 20010725
FDT AU 2000027407 A Based on WO 200043395; BR 2000007720 A Based on WO 200043395; EP 1155019 A1 Based on WO 200043395; JP 2002535332 W Based on WO 200043395
PRAI US 1999-117010P 19990125
TI New substituted **porphyrins** useful for e.g. treating conditions that result from or are exacerbated by oxidant-induced toxicity.
AB WO 200043395 A UPAB: 20020226
NOVELTY - Substituted **porphyrins** (I) are new and useful for e.g. treating conditions that result from or are exacerbated by oxidant-induced toxicity.
DETAILED DESCRIPTION - Substituted **porphyrins** of formula (I) are new.
R1, R3 = are the same and are H, CF3, CO2X, phenyl-4-Y, a group of formula (a)-(i);
R2, R4 = are the same and are a group of formula (a)-(j);
Y = halogen, CO2X;
X = alkyl; and
R5 = H, alkyl;
with the proviso that when R1 and R3 are H then R2 and R4 are not (d); or when R1 and R3 are H and R2 and R4 are (d) the compound is complexed with a metal selected from manganese, iron, copper, colbalt or

nickel.

INDEPENDENT CLAIMS are also included for:

(1) a method of protecting cells from oxidant-induced toxicity comprising contacting cells with (I);

(2) a method of treating a patient suffering from a condition that results from or that is exacerbated by oxidant-induced toxicity comprising administering (I);

(3) a method of treating a pathological condition of a patient resulting from degradation of NO or a biologically active form thereof, comprising administering (I);

(4) a method for treating an inflammatory disease comprising administering (I); and

(5) a method for treating a reperfusion injury comprising administering (I).

ACTIVITY - Antiinflammatory; antiasthmatic; antiarthritic; vasotropic; cerebroprotective; cardiant; tranquilizer; vulnerary; antipsoriatic; dermatological; hypotensive; anti-human immunodeficiency virus; antidiabetic; neuroprotective; antiarteriosclerotic; tocolytic; cytostatic; antimicrobial; gynecological; antioxidant. (5,10,15,20-tetrakis(1,3-dimethylimidazolium-2-yl)porphyrinato)manganese (III) pentachloride (Ia) was used for the treatment of bronchopulmonary dysplasia in baboons delivered prematurely. (Ia) was administered intravenously in a continuous infusion over 10 days. The animal showed marked improvement of the oxygenation index. There was no evidence of clinical decompensation of the lungs at days 9 and 10. This suggests that (Ia) can be used to treat oxidant stress in the premature newborn.

MECHANISM OF ACTION - Modulation of intra- and extracellular levels of oxidants; lipid **peroxidation** inhibitor; NO level regulator; superoxide radical production inhibitor; oxidase inhibitors. (5,10,15,20-tetrtakis(1,3-dimethylimidazolium-2-yl)porphyrinato)manganese (III) pentachloride was used for the treatment of bronchopulmonary dysplasia in baboons delivered prematurely. (Ia) was administered intravenously in a continuous infusion over 10 days. The animal showed marked improvement of the oxygenation index. There was no evidence of clinical decompensation of the lungs at days 9 and 10. This suggests that (Ia) can be used to treat oxidant stress in the premature newborn.

USE - For treating a pathological condition of a patient resulting from degradation of NO, treating a patient suffering from a condition that results from or is exacerbated by oxidant-induced toxicity of protecting cells from oxidant-induced toxicity. For treating inflammatory diseases such as inflammatory lung disease, preferably a bronchopulmonary disease, such as asthma or pulmonary fibrosis (claimed), inflammatory bowel disease, arthritis and vasculitis, reperfusion injury, preferably resulting from a stroke (claimed) or associated with **myocardial infarction**, **coronary** bypass surgery, acute head trauma, organ reperfusion following transplantation, bowel ischemia, hemorrhagic shock, pulmonary **infarction**, surgical occlusion of blood flow and soft tissue injury. (I) can also be used to treat burns and skin diseases such as dermatitis, psoriasis, diseases of the bone, connective tissue disorders, liver cirrhosis and renal diseases, diseases of the cardiovascular system, central nervous system and diseases of musculature, aquired immunodeficiency syndrome, hypertension, **atherosclerosis**, edema, septic shock, pulmonary hypertension, impotence, infertility, endometriosis, premature uterine contractions, microbial infections, gout and diabetes mellitus. (I) can also be used as catalytic scavengers of reactive oxygen species to increase the limited storage viability of transplanted organs and tissues.

Dwg.0/4

L20 ANSWER 10 OF 18 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-303621.[26] WPIDS
CR 2000-350392 [29]
DNC C2000-092152

TI Inhibiting production of mitochondrial reactive oxygen species (ROS), useful e.g. for treating ROS related complications of diabetes.

DC B04

IN BROWNLEE, M

PA (BROW-I) BROWNLEE M

CYC 21

PI WO 2000019993 A2 20000413 (200026)* EN 55p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9964218 A 20000426 (200036)

ADT WO 2000019993 A2 WO 1999-US23457 19991006; AU 9964218 A AU 1999-64218 19991006

FDT AU 9964218 A Based on WO 200019993

PRAI US 1999-305688 19990504; US 1998-167182 19981006

AB WO 200019993 A UPAB: 20000801
NOVELTY - A method (I) for inhibiting the production of mitochondrially derived reactive oxygen species (ROS), is new.

DETAILED DESCRIPTION - A method (I) for inhibiting a cellular pathway, comprising administering (to a cell), an agent which decreases accumulation of mitochondrially derived reactive oxygen species (ROS). The agent is either carbonyl cyanide m-chlorophenylhydrazone, theonyltrifluroactetone and/or manganese tetrakis (benzoic acid) **porphyrin**. The cellular pathway is either PKC (protein kinase C) activation, AGE (advanced glycation end-products) formation, polyol/sorbitol pathway activity, glucosamine pathway activity and/or NFkappaB (undefined) activity.

INDEPENDENT CLAIMS are also included for the following:

(1) a method (II) of screening candidate agents to identify those that are effective at decreasing accumulation of hyperglycemic induced ROS under high glucose conditions, comprising measuring the levels of ROS produced in a cell culture system of insulin-independent cells grown under high glucose conditions in the presence of a candidate agent (the effective agent is identified by a decrease in the level of ROS formed as compared to ROS levels in cell cultures grown under high glucose conditions in the absence of the candidate agent);

(2) a method (III) of screening candidate agents to identify those that are effective at inhibiting mitochondrial electron transport complex under high glucose conditions, comprising measuring the levels of ROS produced in a cell culture system of insulin-independent cells in high glucose in the presence of a candidate agent (the effective agent is identified by a decrease in the levels of ROS formed as compared to ROS levels in cell cultures grown under high glucose conditions in the absence of the candidate agent);

(3) a method (IV) of screening candidate agents to identify those that are effective at dismutating superoxide and/or hydrogen **peroxide** under high glucose conditions, comprising measuring the levels of ROS produced in a cell culture system of insulin-independent cells in high glucose in the presence of a candidate agent (the effective agent is identified by a decrease in the levels of ROS formed as compared to ROS levels in cell cultures grown under high glucose conditions in the absence of the candidate agent);

(4) a method (V) for reducing production of ROS in an insulin-independent blood element exposed to high glucose conditions, comprising contacting the blood element with a compound that inhibits production of hyperglycemia-induced ROS in the blood element by either partially uncoupling oxidative phosphorylation from electron transport in mitochondria, inhibiting a mitochondrial electron transport complex which is a site of ROS generation in the blood element, dismutating superoxide and/or **peroxide** and/or inhibiting binding and activation of hexokinase isoforms to or by the mitochondrial membrane;

(5) a kit containing a packaging material and a composition comprising an agent that will decrease the level of hyperglycemia-induced ROS in insulin-independent cells contained in the packaging material (the

composition is effective at treating diabetic complications and the packaging material is labelled to indicate that it is approved for human use);

(6) a method for decreasing accumulation of ROS in an insulin-independent cell exposed to high glucose conditions, comprising contacting the cell with a composition comprising a superoxide dismutase/catalase mimetic to decrease accumulation of hyperglycemia-induced ROS in the cell; and

(7) a method (VI) for inhibiting glucose-induced activation of a cellular process in an insulin-independent cell, comprising contacting the cell with a composition comprising an agent that decreases accumulation of ROS so that the cellular processes of either PKC activation, AGE formation, polyol/sorbitol pathway activity, glucosamine pathway activity and/or NKkappaB is inhibited.

ACTIVITY - Antidiabetic; vascular active, neuroactive; antisclerotic.

MECHANISM OF ACTION - The production of ROS is inhibited by either partially uncoupling oxidative phosphorylation from electron transport in the mitochondria, inhibiting a mitochondrial electron transport complex which is a site of ROS generation in the cell, dismutating superoxide and/or hydrogen **peroxide** and/or inhibiting binding and activation of hexokinase isoforms to or by the mitochondrial membrane (claimed).

In order to test whether inhibition of mitochondrial ROS overproduction would reverse a diabetes-induced abnormality for which the mechanism is currently undefined, expression of the tyrosine kinase vascular endothelial growth factor receptor Flk-1 was examined. Flk-1 mRNA and protein are both increased in retinae of diabetic rats (see Hammes et al., Diabetes (1998) 47:401-6). In BAE (bovine aortic endothelial cells), 30 mM glucose increased Flk-1 protein levels by 2-fold compared to levels at 5 mM glucose (637 plus or minus 52 versus 329 plus or minus 523 AU). Equal amounts of cell extract protein were used for quantitative immunoblotting (see Giardino et al., J. Clin. Invest. (1996) 97:142228). Flk- 1 was detected using a polyclonal antibody (0.1 mu g/ml). TTFA (thenoyltrifluoroacetone) (10 mu M) completely inhibited 30 mM glucose-induced Flk-1 expression (223 plus or minus 52 AU).

USE - The method (I) may be used for inhibiting the production of mitochondrially derived ROS for the prevention and/or treatment of ROS mediated complications of diabetes or hyperglycemia (e.g. **atherosclerosis**), ROS mediated vascular and/or neurological disease/and or disfunction and age related damage caused by ROS production in mitochondria.

Dwg.0/13

TECH UPTX: 20000531

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Methods: In (II), the insulin-dependent cells are bovine aortic endothelial cells. The accumulation of hyperglycemia-induced ROS is inhibited by either partially uncoupling oxidative phosphorylation from electron transport in the mitochondria, inhibiting a mitochondrial electron transport complex which is a site of ROS generation in the cell, dismutating superoxide and/or hydrogen peroxide and/or inhibiting binding and activation of hexokinase isoforms to or by the mitochondrial membrane. The level of ROS produced is decreased by preventing its formation.

In method (III), the insulin-independent cells are aortic endothelial cells or hepatocytes and the electron transport complex is Complex II.

In (V), the mitochondrial electron transport complex is Complex I or Complex II. The agent is either carbonyl cyanide m-chlorophenylhydrazone, theoyltrifluroacetone, amytal, idebonone and/or manganese tetrakis (benzoic acid) **porphyrin**. The insulin-independent blood element is a cell (e.g. a vascular cell, a peripheral neuron, a circulating blood element (e.g. a platelet, monocyte, a macrophage, a lymphocyte and/or a hepatocyte) and/or a hepatocyte) involved in either vascular and/or neurological disease/dysfunction. Production of hyperglycemia-induced ROS is carried out by normal mitochondria in the insulin-independent blood

element.
In (VI), the agent is either carbonyl cyanide m-chloroohenylhydrazone, theoyltrifluroacetone and/or manganese tetrakis (benzoic acid) **porphyrin**.

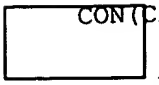
L20 ANSWER 11 OF 18 MEDLINE
AN 2000419086 MEDLINE
DN 20387072 PubMed ID: 10926876
TI **Peroxynitrite** is a major contributor to cytokine-induced **myocardial** contractile failure.
CM Comment in: Circ Res. 2000 Aug 4;87(3):170-2
AU Ferdinandy P; Danial H; Ambrus I; Rothery R A; Schulz R
CS Cardiovascular Research Group, Department of Pharmacology, Heritage Medical Research Center, University of Alberta, Edmonton, Alberta, Canada.
SO CIRCULATION RESEARCH, (2000 Aug 4) 87 (3) 241-7.
Journal code: 0047103. ISSN: 0009-7330.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000906
TI **Peroxynitrite** is a major contributor to cytokine-induced **myocardial** contractile failure.
AB Proinflammatory cytokines depress **myocardial** contractile function by enhancing the expression of inducible NO synthase (iNOS), yet the mechanism of iNOS-mediated **myocardial** injury is not clear. As the reaction of NO with superoxide to form **peroxynitrite** markedly enhances the toxicity of NO, we hypothesized that **peroxynitrite** itself is responsible for cytokine-induced cardiac depression. Isolated working rat hearts were perfused for 120 minutes with buffer containing interleukin-1 beta, interferon-gamma, and tumor necrosis factor-alpha. Cardiac mechanical function and **myocardial** iNOS, xanthine oxidoreductase (XOR), and NAD(P)H oxidase activities (sources of superoxide) were measured during the perfusion. Cytokines induced a marked decline in **myocardial** contractile function accompanied by enhanced activity of **myocardial** XOR, NADH oxidase, and iNOS. Cardiac NO content, **myocardial** superoxide production, and perfusate nitrotyrosine and dityrosine levels, markers of **peroxynitrite**, were increased in cytokine-treated hearts. The **peroxynitrite** decomposition catalyst FeTPPS (5,10,15, 20-tetrakis-[4-sulfonatophenyl]-porphyrinato-iron[III]), the NO synthase inhibitor N(G)-nitro-L-arginine, and the superoxide scavenger tiron each inhibited the decline in **myocardial** function and decreased perfusate nitrotyrosine levels. Proinflammatory cytokines stimulate the concerted enhancement in superoxide and NO-generating activities in the heart, thereby enhancing **peroxynitrite** generation, which causes **myocardial** contractile failure.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Electron Spin Resonance Spectroscopy
Free Radical Scavengers: PD, pharmacology
Heart: DE, drug effects
Heart Failure, Congestive: ME, metabolism
*Heart Failure, Congestive: PP, physiopathology
Inflammation
*Interferon Type II: PD, pharmacology
*Interleukin-1: PD, pharmacology
Muscle Proteins: ME, metabolism
Myocardial Contraction: DE, drug effects
Myocardial Contraction: PH, physiology
Myocardium: ME, metabolism

Myocardium: PA, pathology
NADPH Oxidase: ME, metabolism
*Nitrates: ME, metabolism
Nitric Oxide: ME, metabolism
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitric-Oxide Synthase: ME, metabolism
Nitroarginine: PD, pharmacology
Oxidation-Reduction
Oxidative Stress
Perfusion
Porphyrins: PD, pharmacology
Rats
Rats, Sprague-Dawley
Superoxides: ME, metabolism
Tiron: PD, pharmacology
*Tumor Necrosis Factor: PD, pharmacology
Xanthine Oxidase: ME, metabolism

CN 0 (Free Radical Scavengers); 0 (Interleukin-1); 0 (Muscle Proteins); 0 (Nitrates); 0 (**Porphyrins**); 0 (Tumor Necrosis Factor); EC 1.1.3.22 (Xanthine Oxidase); EC 1.14.13.- (inducible nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 1.6.- (NADPH Oxidase)

L20 ANSWER 12 OF 18 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-023271 [02] WPIDS
DNC C2000-005648
TI New substituted **porphyrins** (e.g. (5,10,15,20-tetrakis-(ethoxycarbonyl)porphyrinato)manganese(III) chloride), useful e.g. for protecting cells from oxidant-induced toxicity and oxidative stress and for treating inflammatory diseases.
DC B02
IN CRAPO, J D; DAY, B; GAUUAN, P J F; PECHULIS, A D; TROVA, M P; DAY, B J
PA (AEOL-N) AEOLUS PHARM INC; (UYDU-N) UNIV DUKE
CYC 87
PI WO 9955388 A1 19991104 (200002)* EN 83p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 9937588 A 19991116 (200015)
EP 1071474 A1 20010131 (200108) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002512989 W 20020508 (200234) 73p
US 6479477 B1 20021112 (200278)
ADT WO 9955388 A1 WO 1999-US8905 19990423; AU 9937588 A AU 1999-37588 19990423; EP 1071474 A1 EP 1999-919995 19990423, WO 1999-US8905 19990423; JP 2002512989 W WO 1999-US8905 19990423, JP 2000-545584 19990423; US 6479477 B1 Provisional US 1998-82881P 19980424, US 1999-296615 19990423
FDT AU 9937588 A Based on WO 9955388; EP 1071474 A1 Based on WO 9955388; JP 2002512989 W Based on WO 9955388
PRAI US 1998-82881P 19980424; US 1999-296615 19990423
TI New substituted **porphyrins** (e.g. (5,10,15,20-tetrakis-(ethoxycarbonyl)porphyrinato)manganese(III) chloride), useful e.g. for protecting cells from oxidant-induced toxicity and oxidative stress and for treating inflammatory diseases.
AB WO 9955388 A UPAB: 20020603
NOVELTY - Substituted **porphyrins** (I) and their salts are new.
DETAILED DESCRIPTION - Substituted **porphyrins** of formula (I) and their salts are new.
R1, R3 = CO2-(1-4C) alkyl or CO2(CH2)nCX3;
X = halo;
n =1-3;

R2, R4 = H, 1-4C alkyl, C O2H, CO2-(1-4C) alkyl, CO2(CH2)nCX3, CON(CH3)2 or CX3; and



P = electron-withdrawing group or H.

ACTIVITY - Antiinflammatory; antiasthmatic; antioxidant.

Male Sprague-Dawley rats were exposed to 100% oxygen, 635 mmHg for 7 days. The animals were injected with a manganic **porphyrin** test compound AEOL-11201 at 15 mg/kg or vehicle intraperitoneally every 24 hours. Perivascular edema, a marker of hyperoxic lung injury, was evaluated on hematoxylin and eosin-stained lung sections. Compared to air control animals, the oxygen exposed group developed significant perivascular edema. AEOL-11201 significantly reduced edema of small-to-medium-sized vessels in oxygen exposed rats.

MECHANISM OF ACTION - Lipid **peroxidation** inhibitors.

USE - Modulate intra- or extracellular levels of oxidants such as superoxide radical, hydrogen **peroxide**, **peroxynitrite**, lipid **peroxides**, hydroxyl radicals and thiyl radicals. Used to protect cells from oxidant-induced toxicity and to treat patients suffering from condition resulting from or exacerbated by oxidant-induced toxicity, pathological conditions resulting from degradation of nitric oxide or biologically active forms, inflammatory diseases including inflammatory lung disease such as bronchopulmonary disease and asthma (claimed). Used as catalytic scavengers to protect against ischemic perfusion injuries associated with **myocardial infarction**, stroke, acute head trauma, organ reperfusion following transplantation, bowel ischemia, hemorrhagic shock, pulmonary **infarction**, surgical occlusion of blood flow and soft tissue injury, to protect against skeletal muscle reperfusion injuries, to protect against damage to the eyes and skin due to sunlight, glaucoma and macular degeneration of the eye, and to treat bone diseases, connective tissue disorders associated with defects in collagen synthesis or degradation and aging. Used to increase limited storage viability of transplanted hearts, kidneys, skin, and other organs and tissues and to inhibit damage due to autooxidation of substances such as food products, pharmaceuticals and stored blood. Used to treat diseases of the central nervous system such as AIDS dementia, stroke, amyotrophic lateral sclerosis (ALS), Parkinson's disease and Huntington's disease), diseases of the musculature (diaphragm diseases such as respiratory failure in emphysema, bronchitis and cystic fibrosis), cardiac fatigue of congestive heat failure, muscle weakness syndromes associated with myopathies, ALS and multiple sclerosis, AIDS, arthritis, systemic hypertension, **arteriosclerosis**, edema, septic shock, pulmonary hypertension (including primary pulmonary hypertension), impotence, infertility, endometriosis, premature uterine contractions, microbial infections, gout, Type II diabetes mellitus and to ameliorate toxic effects associated with endotoxin by preserving vascular tone and preventing multi-organ system damage, inflammations (asthma, adult respiratory distress syndrome including oxygen toxicity, pneumonia including AIDS-related pneumonia, cystic fibrosis, chronic sinusitis, autoimmune diseases, dementias and memory/learning disorders.

ADVANTAGE - Are low molecular weight antioxidants.

Dwg.0/1

L20 ANSWER 13 OF 18 WPIDS (C) 2003 THOMSON DERWENT
AN 1997-077220 [07] WPIDS
CR 1995-161483 [21]; 1998-285680 [25]; 2000-664150 [60]
DNC C1997-024742
TI New **porphyrin**-type oxidant scavengers - used for protecting against oxidants and for modulating biological processes involving oxidants..
DC B02 D16
IN BATINIC-HABERLE, I; CRAPO, J D; DAY, B J; FOLZ, R J; FREEMAN, B A; FRIDOVICH, I; OURY, T; TROVA, M P
PA (UYAL-N) UNIV ALABAMA; (UYDU-N) UNIV DUKE; (UYAL-N) UNIV ALABAMA BIRMINGHAM RES FOUND; (TROV-I) TROVA M P

CYC 23
PI WO 9640223 A1 19961219 (199707)* EN 195p
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA IL JP
AU 9663870 A 19961230 (199716)
EP 831891 A1 19980401 (199817) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 11509180 W 19990817 (199943) 172p
US 5994339 A 19991130 (200003)
AU 725602 B 20001012 (200055)
AU 2000053511 A 20001130 (200101)#
ADT WO 9640223 A1 WO 1996-US10497 19960607; AU 9663870 A AU 1996-63870 19960607; EP 831891 A1 EP 1996-923328 19960607, WO 1996-US10497 19960607; JP 11509180 W WO 1996-US10497 19960607, JP 1997-502304 19960607; US 5994339 A CIP of US 1993-136207 19931015, CIP of US 1994-322766 19941013, US 1995-476866 19950607; AU 725602 B AU 1996-63870 19960607; AU 2000053511 A Div ex AU 1996-63870 19960607, AU 2000-53511 20000821
FDT AU 9663870 A Based on WO 9640223; EP 831891 A1 Based on WO 9640223; JP 11509180 W Based on WO 9640223; AU 725602 B Previous Publ. AU 9663870, Based on WO 9640223; AU 2000053511 A Div ex AU 725602
PRAI US 1996-613418 19960311; US 1995-476866 19950607; US 1993-136207 19931015; US 1994-322766 19941013; AU 2000-53511 20000821
TI New **porphyrin**-type oxidant scavengers - used for protecting against oxidants and for modulating biological processes involving oxidants..
AB WO 9640223 A UPAB: 20001230
Oxidant scavengers are claimed comprising a nitrogen contg. macrocyclic moiety and a cell surface or extracellular matrix targeting moiety, or their salts. More specifically the scavengers are of formula (I), where R1 is a bond, cyclohexylene, 1,4-pyridiniumylene, phenylene or phenylene substd. with NO2, SO3H, SO3-, X or Y; X = halogen; Y = alkyl; R2 is a bond, -(CY'2)n-, -(CY'2-CY'=CY')n-, -(CY'2 - CY'2-CH=CH)n-, -(CY'=CY')n-, or -(CY'2-C=O)n-; Y' = H or alkyl; n is 1 to 8; and R3 is -Y'', -OH, -NH2, -N+(Y'')3, -COOH, -COO-, -SO3H, -SO3-, -C-PO3H-; Y'' = alkyl; when R1 is 1,4-pyridiniumylene and R2 is a bond, R3 is not Y''; and when R1 is phenylene and R2 is a bond, R3 is not -Y'', -N+(Y'')3 or COOH.

Also claimed is a method of treating a pathological condition resulting from degradation of NO. or resulting from **peroxynitrite** accumulation, comprising administering a cpd. having the activity of a catalytic antioxidant.

Further claimed, inter alia, is an isolated EC-SOD gene having a defined sequence of 10079 bases or portion of at least 18 nucleotides in length.

USE - The oxidant scavengers can be used for protecting against the deleterious effects of oxidants and for modulating biological processes involving oxidants. They can be used for eg. treating inflammatory conditions, treating disorders resulting from aberrant smooth muscle function or to protect against ischaemia reperfusion injuries associated with **myocardial infarction**, stroke, acute head trauma, organ reperfusion following transplantation, bowel ischaemia, pulmonary **infarction**, surgical occlusion of blood flow, and soft tissue injury. They can further be used to protect against damage to the eye due to sunlight (and to the skin) as well as glaucoma, and macular degeneration of the eye. Diseases of the bone are also amenable to treatment with the cpds. Further, connective tissue disorders associated with defects in collagen synthesis or degradation can be treated with the cpds.

ADVANTAGE - In the oxidant scavengers, substits. can be selected to render them resistant to degradation by haemoxygenase and also so that they do not interfere with normal **porphyrin** metabolism, can pass through cell membranes and bind to cell surface or extracellular matrix elements.

Dwg.0/42

TT TT: NEW **PORPHYRIN** TYPE OXIDANT SCAVENGER PROTECT OXIDANT MODULATE BIOLOGICAL PROCESS OXIDANT.

L20 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2003 ACS
AN 1997:54968 CAPLUS
DN 126:116450
TI Selective resistance of LDL core lipids to iron-mediated oxidation. Implications for the biological properties of iron-oxidized LDL
AU Tribble, Diane L.; Chu, Berbie M.; Levine, Gerri A.; Krauss, Ronald M.; Gong, Elaine L.
CS Lawrence Berkeley National Lab., Univ. California, Berkeley, CA, 94720, USA
SO Arteriosclerosis, Thrombosis, and Vascular Biology (1996), 16(12), 1580-1587
CODEN: ATVBFA; ISSN: 1079-5642
PB American Heart Association
DT Journal
LA English
AB Although the nature and consequences of oxidative changes in the chem. constituents of low d. lipoproteins (LDLs) have been extensively examd., the phys. dynamics of LDL oxidn. and the influence of phys. organization on the biol. effects of oxidized LDLs have remained relatively unexplored. To address these issues, in the present studies the authors monitored surface- and core-specific peroxidative stress relative to temporal changes in conjugated dienes (CDs), particle charge (an index of oxidative protein modification), and LDL-macrophage interactions. Peroxidative stress in LDL surface and core compartments was evaluated with the site-specific, oxidn.-labile fluorescent probes parinaric acid (PnA) and PnA cholesteryl ester (PnCE), resp. When oxidn. was initiated by Cu2+, oxidative loss of the core probe (PnCE) closely followed that of the surface probe (PnA), as indicated by the time to 50% probe depletion (t1/2; 15.5 and 30.4 min for PnA and PnCE, resp.). Both probes were more resistant in LDL exposed to Fe3+ (t1/2, 53.2 and 346.7 min), although core probe resistance was much greater with this oxidant (PnCE t1/2/PnA t1/2. 5.8 vs. 2.0 for Cu2+). Despite differences in the rate and extent of oxidative changes in Cu2+ vs. Fe3+- exposed LDLs, PnCE loss occurred in close correspondence with CD formation and appeared to precede changes in particle charge under both conditions. Exposure of LDLs to hemin, a lipophilic Fe3+-contg. **porphyrin** that becomes incorporated into the LDL particle, resulted in rapid loss of PnCE and simultaneous changes in particle charge, even at concns. that yielded increases in CDs and thiobarbituric acid-reactive substances similar to those obtained with free Fe3+. These results suggest that oxidn. of the LDL hydrophobic core occurs in conjunction with accelerated formation of CDs and may be essential for LDL protein modification. In accordance with the known effects of oxidative protein modifications on LDL receptor recognition, exposure of LDLs to Cu2+ and hemin but not Fe3+ produced particles that were readily processed by macrophages. Thus, the phys. site of oxidative injury appears to be a crit. determinant of the chem. and biol. properties of LDLs, particularly when oxidized by Fe3+.
IT Lipoprotein receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(LDL; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)
IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(blood, lipoprotein; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage

interactions, and **atherosclerosis**)

IT **Peroxidation**
(lipid; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

IT Lipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(low-d., oxidized; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

IT Lipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(low-d.; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

IT Stress, animal
(**peroxidative**; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**peroxidn.**; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(polyunsatd., conjugated; selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

IT Macrophage
(selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

IT 7439-89-6, Iron, biological studies 7440-50-8, Copper, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(selective resistance of human LDL core lipids to iron-mediated oxidn. in relation to copper-mediated oxidn., **peroxidative** stress, conjugated dienes, macrophage interactions, and **atherosclerosis**)

L20 ANSWER 15 OF 18 WPIDS (C) 2003 THOMSON DERWENT
AN 1996-010678 [01] WPIDS
CR 2001-474956 [41]
DNC C1996-003333
TI Peroxy nitrite decomposition by metal **porphyrin**(s) and aza macrocycle(s) - use in treatment of diseases affected by oxygen radicals, e.g., cancer, ischaemia, inflammation, sepsis, stroke, parkinsonism.
DC B02
IN SALVEMINI, D; STERN, M K

PA (MONS) MONSANTO CO
CYC 64
PI WO 9531197 A1 19951123 (199601)* EN 68p
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG
W: AM AU BB BG BR BY CA CN CZ EE FI GE HU IS JP KG KR KZ LK LR LT LV
MD MG MN MX NO NZ PL RO RU SG SI SK TJ TM TT UA US UZ VN
AU 9525120 A 19951205 (199620)
NO 9604793 A 19970106 (199711)
EP 758892 A1 19970226 (199714) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
FI 9604537 A 19970110 (199715)
BR 9507643 A 19970923 (199745)
CZ 9603234 A3 19971015 (199748)
HU 76327 T 19970828 (199811)
JP 10500671 W 19980120 (199813) 83p
KR 97703143 A 19970703 (199829)
NZ 285648 A 19990828 (199939)
AU 709553 B 19990902 (199948)
MX 9605560 A1 19980201 (199954)
CN 1152871 A 19970625 (200134)
ADT WO 9531197 A1 WO 1995-US5886 19950509; AU 9525120 A AU 1995-25120 19950509; NO 9604793 A WO 1995-US5886 19950509, NO 1996-4793 19961112; EP 758892 A1 EP 1995-919143 19950509, WO 1995-US5886 19950509; FI 9604537 A WO 1995-US5886 19950509, FI 1996-4537 19961112; BR 9507643 A BR 1995-7643 19950509, WO 1995-US5886 19950509; CZ 9603234 A3 WO 1995-US5886 19950509, CZ 1996-3234 19950509; HU 76327 T WO 1995-US5886 19950509, HU 1996-3140 19950509; JP 10500671 W JP 1995-529755 19950509, WO 1995-US5886 19950509; KR 97703143 A WO 1995-US5886 19950509, KR 1996-706414 19961113; NZ 285648 A NZ 1995-285648 19950509, WO 1995-US5886 19950509; AU 709553 B AU 1995-25120 19950509; MX 9605560 A1 MX 1996-5560 19961112; CN 1152871 A CN 1995-194075 19950509
FDT AU 9525120 A Based on WO 9531197; EP 758892 A1 Based on WO 9531197; BR 9507643 A Based on WO 9531197; CZ 9603234 A3 Based on WO 9531197; HU 76327 T Based on WO 9531197; JP 10500671 W Based on WO 9531197; KR 97703143 A Based on WO 9531197; NZ 285648 A Based on WO 9531197; AU 709553 B Previous Publ. AU 9525120, Based on WO 9531197
PRAI US 1994-242498 19940513
TI Peroxy nitrite decomposition by metal **porphyrin**(s) and aza macrocycle(s) - use in treatment of diseases affected by oxygen radicals, e.g., cancer, ischaemia, inflammation, sepsis, stroke, parkinsonism.
AB WO 9531197 A UPAB: 20010914
Method of treating a disease ameliorated by decomposition of **peroxynitrite** (PON) at a rate faster than its natural background decay rate, by admin. of a metal complex PON decomposition catalyst; is new.

USE - PON decomposition produces harmful free radicals, e.g. oxygen, and superoxide dismutase (SOD), a normal detoxication enzyme, can be overloaded and inactivated; the decomposition catalysts cause PON decomposition instead to benign species. The catalysts are of use for treatment of reperfusion injury after ischaemia, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, hypertension, psoriasis, organ transplant rejection or preservation, impotence, radiation induced injury, asthma, **atherosclerosis**, thrombosis, platelet aggregation, side effects of cancer metastasis or interleukin therapy, influenza, stroke, burns, trauma, pancreatitis, pyelonephritis, hepatitis, autoimmune diseases, insulin dependent diabetes, intravascular coagulation, fatty embolism, adult and infantile respiratory distress, and neonate haemorrhages.

Dwg.0/10
TT TT: PEROXY NITRITE DECOMPOSE METAL **PORPHYRIN** AZA MACROCYCLE TREAT DISEASE AFFECT OXYGEN RADICAL CANCER ISCHAEMIC INFLAMMATION SEPTIC STROKE PARKINSON.

L20 ANSWER 16 OF 18 MEDLINE
AN 95084221 MEDLINE
DN 95084221 PubMed ID: 7992105
TI Photosensitizers in photodynamic therapy.
AU Levy J G
CS Quadra Logic Technologies, Inc, Vancouver, British Columbia, Canada.
SO SEMINARS IN ONCOLOGY, (1994 Dec) 21 (6 Suppl 15) 4-10.
Journal code: 0420432. ISSN: 0093-7754.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199501
ED Entered STN: 19950124
Last Updated on STN: 19980206
Entered Medline: 19950112
AB Photodynamic therapy (PDT) is based on the use of light-sensitive molecules called photosensitizers. Photoactivation causes the formation of singlet oxygen, which produces **peroxidative** reactions that can cause cell damage and death. Porfimer sodium (Photofrin, manufactured by Lederle Parenterals, Carolina, Puerto Rico, under license from Quadra Logic Technologies, Inc, Vancouver, BC, Canada) is the photosensitizer that has been studied most extensively. Patients generally have to be hospitalized for 2 days prior to light treatment after administration of porfimer sodium; it takes approximately 48 hours after injection to reach optimal concentration in tumor tissue. The tumoricidal capacity of PDT with porfimer sodium is determined in part by the maximum depth of penetration of light having a wavelength of 630 nm. Porfimer sodium causes cutaneous photosensitivity that may last for up to 6 weeks. Benzoporphyrin derivative (BPD verteporfin; BPD-Quadra Logic Technologies, Inc, Vancouver, BC, Canada), another photosensitizer, accumulates more rapidly in tumor tissue, permitting optimal PDT 30 to 150 minutes following intravenous administration. It is rapidly cleared from the body, and skin photosensitivity does not extend beyond a few days. The primary mechanism of action of PDT is related to the selective accumulation of photosensitizers in cancer tissue. Photodynamic therapy also shows promise in the treatment of a number of nonneoplastic conditions, including psoriasis, macular degeneration of the retina, **atherosclerotic** plaque and restenosis, bone marrow purging for treatment of leukemias with autologous bone marrow transplantation, inactivation of viruses in blood or blood products, and several autoimmune conditions, including rheumatoid arthritis. Physiologic characteristics shared by this disparate group of diseases, and the mechanisms by which they may mediate photoactivation, are discussed.
CT Check Tags: Human
Antiviral Agents: TU, therapeutic use
Arteriosclerosis: DT, drug therapy
Autoimmune Diseases: DT, drug therapy
Bone Marrow Purging
Hematoporphyrin Derivative: AD, administration & dosage
Hematoporphyrin Derivative: TU, therapeutic use
Macular Degeneration: DT, drug therapy
*Neoplasms: DT, drug therapy
*Photochemotherapy
Photosensitizing Agents: AD, administration & dosage
*Photosensitizing Agents: TU, therapeutic use
Porphyrins: AD, administration & dosage
Porphyrins: TU, therapeutic use
Psoriasis: DT, drug therapy
Radiation-Sensitizing Agents: AD, administration & dosage
Radiation-Sensitizing Agents: TU, therapeutic use
Skin: DE, drug effects
Skin: RE, radiation effects

Time Factors
RN 129497-78-5 (verteporfin); **68335-15-9 (Hematoporphyrin Derivative)**
CN 0 (Antiviral Agents); 0 (Photosensitizing Agents); 0 (**Porphyrins**); 0 (Radiation-Sensitizing Agents)

L20 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2003 ACS
AN 1992:53894 CAPLUS
DN 116:53894
TI Identification of initiating agents in myoglobin-induced lipid peroxidation
AU Newman, Emma S. R.; Rice-Evans, Catherine A.; Davies, Michael J.
CS Dep. Biochem., St. Thomas' Hosp., London, SE1 7EH, UK
SO Biochemical and Biophysical Research Communications (1991), 179(3), 1414-19
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB A considerable no. of previous studies have demonstrated that metmyoglobin can initiate damage to biol. mols., free fatty acids and isolated membranes in the presence of either hydrogen **peroxide** or alkyl hydroperoxides, and it has been suggested that such reactions may be important in the development of **myocardial** damage resulting from reperfusion after a period of ischemia [1-6]. The reaction of metmyoglobin with **peroxides** has been shown to involve the formation, possibly via the generation of a **porphyrin** radical-cation species (**Porphyrin**+.cntdot.-FeIV:O), of a ferryl (iron(IV)-oxo, FeIV:O) intermediate and a protein radical (reactions 1 & 2) [7-9]. Subsequent reactions result, ultimately, in damage to the heme and the release of iron ions which could react with excess **peroxide** to give further radicals (e.g. HO.cntdot. from H2O2 and RO.cntdot. and ROO.cntdot. from alkyl hydroperoxides) [3,5,10,11].

L20 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2003 ACS
AN 1991:532825 CAPLUS
DN 115:132825
TI Lipid peroxidation and cellular functions: in vitro models and relation to in vivo observations
AU Maziere, J. C.; Salmon, S.; Santus, R.; Candide, C.; Reyftmann, J. P.; Morliere, P.; Maziere, C.; Dubertret, L.
CS Lab. Biochim., Fac. Med. Saint-Antoine, Paris, Fr.
SO NATO ASI Series, Series A: Life Sciences (1990), 189(Free Radicals, Lipoproteins, Membr. Lipids), 327-42
CODEN: NALSDJ; ISSN: 0258-1213
DT Journal; General Review
LA English
AB A review with 60 refs. The consequences of lipid **peroxidn.** on various cell metabs. are reviewed with special emphasis on low-d. lipoprotein catabolism and its relation to **atherosclerosis.** Results concerning an original model developed for the study of the effects of singlet oxygen on lipid **peroxidn.** are also presented. In this exptl. model, lipoproteins are used as a lipidic environment for **porphyrins** generating singlet oxygen during their photoactivation. Singlet oxygen attack results in the appearance of fatty acid and cholesterol **peroxidn.** products and in alterations of apolipoproteins, but that apolipoprotein alterations markedly differ between low-d. and high-d. lipoproteins. Besides its theor. interest for the study of lipid oxidn. in lipid-protein complexes, this model brings new data concerning the consequences of the photoactivation of anticancer **porphyrins** which are carried by plasma lipoproteins, mainly LDL and HDL.
ST review lipid **peroxidn** cell metab **atherosclerosis**
IT **Atherosclerosis**
(low-d. lipoprotein metab. induced by **peroxidn.** in relation

to, in humans and lab. animals)

IT **Peroxidation**
(of lipids, cell metab. response to, **atherosclerosis** in relation to, in humans and lab. animals)

IT Lipids, biological studies
RL: BIOL (Biological study)
(**peroxidn.** of, cell metab. response to, **atherosclerosis** in relation to, in humans and lab. animals)

IT Lipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(low-d., metab. of, **peroxidn.**-induced, **atherosclerosis** in relation to, in humans and lab. animals)